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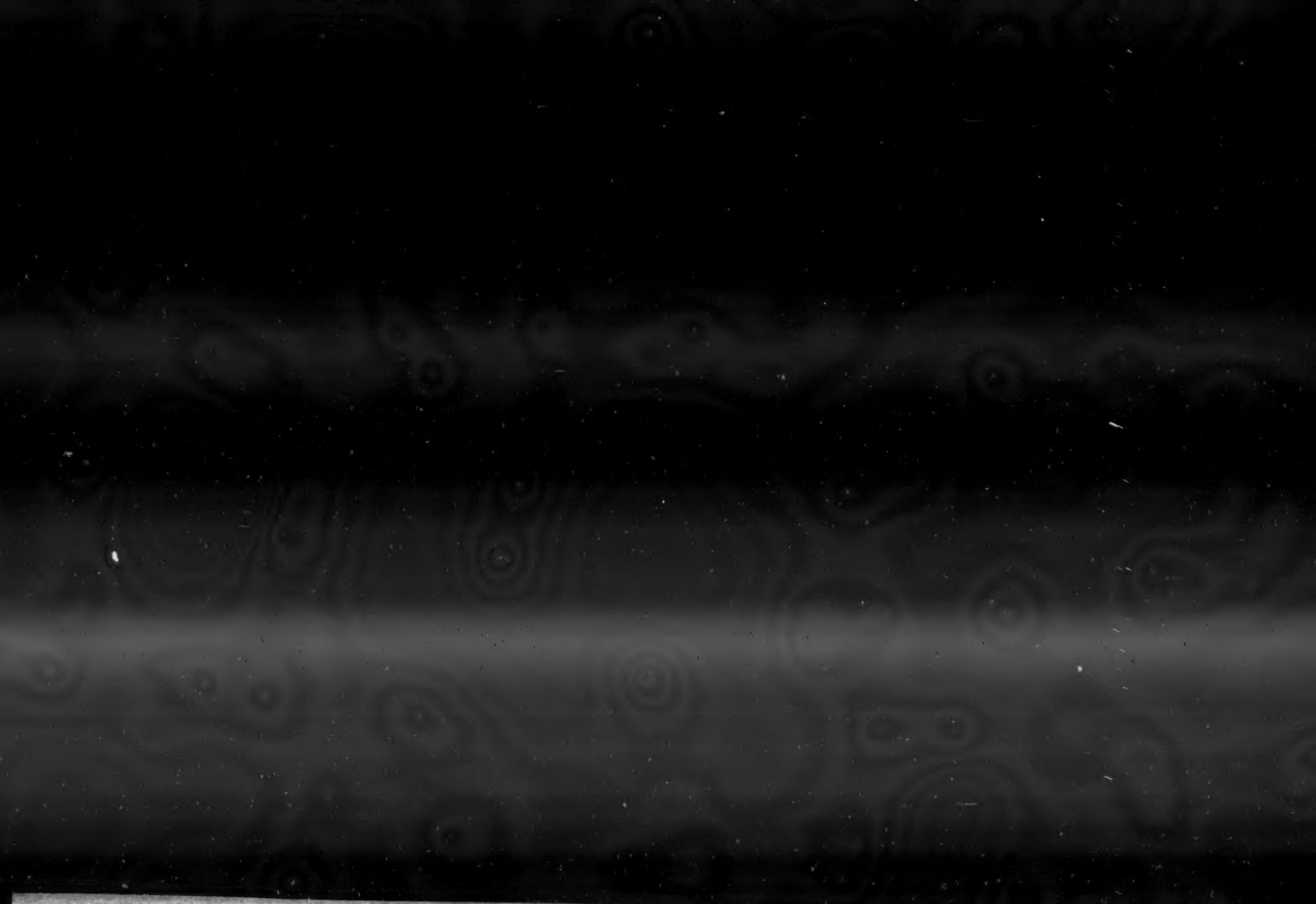

Section of Neurology

President—ANTHONY FEILING, M.D.

[*February* 17, 1938]

CASES SHOWN AT THE NATIONAL HOSPITAL, QUEEN SQUARE, LONDON.

Spasmodic Torticollis: Spastic Dysarthria: Tremor.—MACDONALD CRITCHLEY, M.D.

L. J. L., male, aged 28. Single.

Family history and previous health.—Nothing relevant.

In 1932, while the patient was in the Navy, a tremor developed in the left hand. The case was diagnosed shortly afterwards as one of disseminated sclerosis and the man was discharged from the Service.

In 1934, he developed spasmodic movements of the head and neck towards the left side. The tremor in the left arm was now worse. Trouble with the speech appeared for the first time.

On examination.—Spasmodic torticollis with movements of the chin upwards and to the left; clonic twitchings of the right corner of the mouth. Rhythmic tremor of the left hand, increased on voluntary movement. Knee-jerks present, ankle-jerks absent. Plantar reflexes flexor; abdominal reflexes present. Optic discs perhaps unduly pale over the temporal halves. All forms of sensation somewhat reduced over the left half of the body. Speech: jerky and hoarse; apparent inco-ordination between the muscles of respiration and of articulation. Both vocal cords move well on phonation, but ventricular bands do not come into apposition. Cerebrospinal fluid normal in composition and pressure.

October 1937: Section of right spinal accessory nerve, without much relief as regards the torticollis.

Dr. CRITCHLEY said that this patient exhibited a train of symptoms which he had seen in combination several times previously. No adequate account existed in the literature so far as he knew, but various diagnostic labels had incorrectly been applied to these cases, chiefly "disseminated sclerosis" and "double athetosis".

Their most interesting and striking feature was the curious affection of speech, which was not easy to describe. At times the dysarthria had been termed "inspiratory speech" but this expression was wholly incorrect. Schuster spoke of "sea-lion speech" which still did not adequately indicate the curious, constrained, breathless and spastic dysarthria, almost as though the patient were being throttled.

A Variant of Epiloia. Adenoma Sebaceum, without Epilepsy, in a Woman: Epilepsy without Adenoma Sebaceum in her Son.—D. DENNY-BROWN, M.B.

W. E., male, aged 23, came for advice about attacks of excitement and restlessness which he had had for nine months. He had had convulsions for a brief interval at the age of 3, but had had none since that age. There had been no previous illness of note; he had had a mild head injury at the age of 9, and he had always been "rather backward", though he had attained Standard VI at the age of 14 when he left school.

The attacks complained of were of strange behaviour. He would be found in bed in a restless state. He would keep stammering, and would not answer. On one occasion he got out of bed and wandered as if looking for something, came back with a tray of tea-things for his mother but had not added the water to the tea leaves, went back and was found to have fried some bread later. He then said he could not find an egg. When one was pointed out to him he appeared not to see it and said: "All the chickens have flown away". He was restless, bewildered, and excited, running in and out of the kitchen, and he spoke very little, though his speech was

normal. He then suddenly ran out of the house and to the railway station—so rapidly that he could not be followed. He cannot recall any of these events and remembers only reaching a ticket-collector at another station, finding that he had no ticket, and not knowing how he had entered the train which brought him.

In the above attacks no kind of convulsive onset was known of by the relatives, and he was found in the attack in the early morning on each occasion. He had had about one attack a month. For the previous month he had had nocturnal enuresis once a week, though never before.

In response to questions it was stated that he had been liable to brief attacks in which he did not notice what had been said. These "vacant" turns had occurred two or three times a week for a year, and in some he would spin round. The attack lasted only a few seconds. His intelligence had become less in the previous year; he had become forgetful, and was liable to make childish remarks. He was slower in his actions.

On examination.—Slow in thought and action; lacks initiative. Memory poor; arithmetic bad; only retains five figures in the retention test. Forgot name-address flower test completely. Insight impaired. Showed no abnormal physical signs, and in particular has no trace of adenoma sebaceum. He has several brown moles on the face, and two *café-au-lait* patches on the body. No retinal changes. Lumbar puncture showed cerebrospinal fluid under normal pressure, containing 4 cells per c.mm., protein 0·075%, globulin negative, Lange no change, Wassermann reaction negative. Blood Wassermann reaction negative. X-rays show no abnormality of skull. Two attacks of generalized brief tonic-clonic convulsion were observed at night.

Since discharge from hospital he has been completely free from attacks of any kind, and is much brighter mentally, as a result of treatment by luminal.

The patient's mother, aged 52, has a profuse rash of adenoma sebaceum on both cheeks. She has never suffered from epilepsy. She is vague and inclined to be garrulous, and her intelligence appears to be subnormal. The patient is her only son. She is one of a family of seven. The eldest brother is alive and well, aged 57. The next brother died in infancy. A younger sister, aged 42, also suffers from adenoma sebaceum. Two younger sisters, aged 40 and 38, and the youngest brother, aged 35, are alive and well, and have no adenoma sebaceum. The second youngest brother died in the European War. The two sisters affected with adenoma sebaceum have had it as long as they can remember. None of this generation suffered from epilepsy. The father of this family died in a mental hospital, from the effects of alcoholism. He is said not to have suffered from either epilepsy or adenoma sebaceum.

Discussion.—Dr. DENNY-BROWN said it was a moot point whether this was a progressive condition in the son. Minor forms of a number of conditions were not apparently progressive. There was no neurofibromatosis in these cases, but he thought that pigmented moles and *café-au-lait* patches might indicate a relation to that condition.

Dr. F. PARKES WEBER said there was no proof in the literature that neurofibromatosis was really related to tuberous sclerosis of the brain. Many ordinary persons were found to have a few *café-au-lait* spots if examined very carefully.

Dr. H. G. GARLAND said that in the large number of cases of neurofibromatosis which he had collected he had never seen anything in them like the association now presented. He had also collected a number of cases of neurofibromatosis in which the condition was obviously inherited and was strictly a Mendelian dominant. But in cases of epiloia there was rarely any evidence of dominant inheritance.

"Rubral Tremor."—D. DENNY-BROWN, M.B.

A. J. M., aged 68.

Shaking of the left arm began at the age of 45, and since that time has very gradually involved all the limbs. One of six paternal uncles developed a senile tremor

at the age of 80, but no other members of the family have suffered from any nervous complaint.

On examination.—There is a regular tremor of the upper and lower limbs, and occasionally of the tongue, of the rhythm of the tremor of Parkinsonism, and occurring at rest. The tremor is slightly increased by movement, and affects the peripheral parts of the limbs more than the proximal. There is no rigidity and no blepharoclonus. The patient lacks ability to converge the eyes. Reflexes normal.

Though closely resembling the tremor of paralysis agitans, and in fact carrying this diagnosis from 1923 to 1937, the condition is progressing much more slowly and is obviously much less disabling. The above name is suggested because of the similarity between this tremor and that of Benedict's syndrome, and because the affection appears to be related to degeneration of an extrapyramidal kind.

Spasmodic Choreo-Athetosis.—J. W. ALDREN TURNER, M.B.

Male, aged 19.

History.—When he began to walk, at the age of 2 years, he was noticed to be dragging the left leg, and at about the same time the left arm was noticed to be weak. At the age of 8 or 9 involuntary movements started in the left arm and leg, and these have gradually become worse, especially during the last three years, so that now the patient has difficulty in doing things for himself.

Family history.—Five siblings. No history of similar disorder.

On examination.—A left hemiplegia of slight degree with typical reflex changes, and a pes cavus. No sensory changes. The tone is increased in the left arm and leg.

Involuntary movements: For long periods the patient will lie still without involuntary movements, but when a stranger enters the ward or if he becomes excited the movements begin. They are explosive in character and are so violent that the patient sometimes falls out of his chair and has often bruised his limbs. They are of a wild choreiform type and are strictly confined to the left arm and leg; the trunk is not affected.

Treatment.—7.10.37: Operation by Mr. Geoffrey Jefferson. The motor cortex was exposed and appeared to be normal. By stimulation the arm area was found and a sub-pial excision of this convolution was carried out, leaving a thin strip just in front of the Rolandic sulcus. The left arm was completely paralysed after this and there were no involuntary movements, but as power returned the movements returned, possibly a little less violent than before.

25.11.37: Anterior chordotomy was performed on the left side at C 2 level by Mr. Jefferson. Again there was temporary cessation of movements, but they returned after a day or two. On the whole they are less violent than when the patient was admitted to hospital.

The PRESIDENT said that this case, like many others of the kind, demonstrated at least one thing about this type of movement, namely that the functional activity of the cortex seemed to be necessary for its production. He would suggest a bolder and deeper extirpation of the motor cortex. If the brachial plexus were cut right through, no doubt a cessation of movement would be obtained, but there would be a permanent paralysis of the arm, and that was rather a confession of failure. He thought that something more radical might be done in the cortex.

Mucocœle of Frontal Sinus.—J. W. ALDREN TURNER, M.B.

Male, aged 35.

History.—Two years ago the patient noticed drooping of the right eyelid, but this did not trouble him much. A few months ago the eyelid seemed to be drooping more; he began to see double when he looked upwards, and he had some pain above the eye. Since then he has noticed that the eye waters in the morning and that the vision in this eye is failing. He has not suffered from nasal catarrh.

On examination.—Vision: Right, $\frac{6}{24}$; left, $\frac{6}{6}$. Fundi normal.

The right eyeball is displaced downwards and there is some proptosis. Upward movement of this eye is impaired ; there is diplopia on looking upward. On palpation a firm mass, apparently attached to the bone, can be felt above and to the inner side of the eye.

The corneal reflexes are equal and there is no sensory loss over the area of the 5th-nerve distribution. X-rays show an opaque right antrum, a large right frontal sinus, and erosion of the roof of the right orbit.

The Grasp Reflex in a Hand with No Power of Voluntary Closure.—A. M. STEWART-WALLACE, M.B.

Male, aged 64. Left frontal meningioma removed fourteen years ago. There is a severe right hemiplegia associated with such profound loss of voluntary power that the patient cannot clench the fingers or imitate voluntarily the grasp which can be so readily provoked reflexly. Tactile stimuli alone with cotton-wool will produce involuntary closure of the hand, a response which is abolished by regional novocain anæsthesia of the median and ulnar nerves. Firmer objects involving proprioceptive stimuli to the muscles and tendons also cause reflex closure, which persists after novocain anæsthesia. In the same way the involuntary tightening and persistence of the grasp on attempted withdrawal of an object can be initiated and maintained by either tactile or proprioceptive stimuli alone. Certain features about the manner in which the maximum response is obtained suggest that, though the response is unquestionably involuntary and devoid of all volitional control, the phenomenon is more complicated than a simple spinal reflex.

Discussion.—Dr. GARLAND said he noticed that the patient during the demonstration had been fiddling with his hand, and during that time he had not the grasp reflex. He wondered whether the voluntary act could be eliminated.

Dr. STEWART-WALLACE said that with external objects reflex could also be inhibited when the hand was held passively in an extended position.

Dr. DENNY-BROWN said that the difference between what was called reflex and what might be called essentially a movement on the conscious level was only with certainty determined by the occurrence of the movement without the possibility of willed effort. Thus the reflexes of experimental animals were certainly reflexes when they could be demonstrated after decortication or its equivalent. This was not to say that there were not reflexes which involved the cerebral cortex. There was good ground for believing, for instance, that fixation of the eyes was a reflex, yet its mechanism involved the visual cortex. He thought that the grasp reflex was a true reflex because occasionally he had seen it where there was no ability to grasp the hand voluntarily, where this reaction could be brought about automatically, and repeated by a particular stimulus on different occasions. In his observation the phase of preservation of the reaction without ability for willed movement in the hand had been a passing and transitory event. Dr. Stewart-Wallace had demonstrated this phase in a patient who had exhibited it considerably over a long period and he was glad members had had an opportunity of seeing it.

In the combination of tactile and proprioceptive factors usually necessary in an adequate stimulus for the reaction, the grasp reflex closely resembled the extensor thrust and the "positive supporting reaction", a progression reflex and a body-righting reflex respectively, in quadripedal mammals. The grasp reflex of the thalamic monkey could legitimately be aligned with the righting reflexes. Reflex grasping in response to moving contact could be quite distinct from random grasping and groping movements, and it was only in this respect that he considered the phenomenon truly reflex and of localizing value.

Painful Phantom Upper Limb.—A. M. STEWART-WALLACE, M.B.

Male, aged 61. Arm crushed in motor accident in July 1934. Arm amputated at shoulder-joint four hours later. A painful phantom limb appeared nine weeks after the operation, the distal portion being felt before the proximal parts.

October 1935 : Alcohol injected into the brachial plexus. This was followed by three weeks' temporary relief from pain, but by permanent loss of the ability previously present to change the posture of the phantom limb.

February 1936: Small nodule in stump dissected free and nerve injected with alcohol. Temporary relief from pain for three weeks.

March 1936: A left rhizotomy of the left posterior roots C 5–T 1. Temporary relief for two weeks, after which the pain returned and was more severe than ever.

April 1936: Right chordotomy at C 2, with good analgesia below C 2 on the left side. The whole phantom limb and all pain disappeared, but suddenly, seven weeks later, the pain returned. It was worse than before, and has persisted since.

The phantom limb lies rigidly behind the back and is associated with a constant dull burning pain and also with periodic cramps radiating downwards from the shoulder.

Discussion.—Dr. STEWART-WALLACE (in reply to a question as to whether the patient had received compensation) said that a weekly payment had been made to him until two years after the accident, and then he had received a lump sum.

Dr. MACDONALD CRITCHLEY said he thought that the phantom sensations—he was now speaking only of the painless examples—faded with the passage of time. This, however, did not invariably happen. Not long ago he had seen a man of 84 who had lost his leg at the age of 16, and was still conscious of a phantom limb, which, however, was never painful. The phantom limb had receded in space, and was now referred to about the level of the knee. He could not say what was the likelihood of persistence in painful cases.

Unusual Coincidence of Bitemporal Hemianopia and Papillœdema, due to an Adamantinoma.—W. R. HENDERSON, F.R.C.S.

J. D., a boy, aged 7, admitted under the care of Dr. C. P. Symonds.

History.—For two years the patient has had frequent attacks of severe frontal headache, especially around the left eye; these were accompanied by vomiting. Three weeks ago he attended as an out-patient at Guy's because of attacks of bronchitis, and was admitted for an investigation of the headache and vomiting.

The visual defect was discovered on examination; he had not noticed it previously.

On examination.—A rather undersized but very bright and intelligent boy.

Vision: Left, finger counting; right, $\frac{6}{6}$. Fields: Complete bitemporal hemianopia. Fundi: Early bilateral papillœdema; optic discs congested with blurred edges and very distended veins; no atrophy.

Cranium: Well-marked cracked-pot percussion note.

X-ray findings: Moderate hammer-marking on the vault and early separation of sutures; large ballooned sella with a short line of fine mottled calcification lying immediately in front of and above the dorsum sellæ which is displaced backwards.

The chief reasons against the diagnosis of pituitary adenoma were the patient's age (he was too young) the increased intracranial pressure, the minute calcification and the papillœdema.

Operation (11.11.37, by Mr. Geoffrey Jefferson).—The question was whether the tumour should be approached from the front—because of the bitemporal hemianopia, or from above—through the lateral ventricle—because of the papillœdema. Mr. Jefferson thought that the more important sign in this case was the bitemporal hemianopia, and the subfrontal extradural approach to the chiasmal region was chosen. The tumour was a cystic adamantinoma from which 15 c.c. of fluid were aspirated. Part of the cyst wall was removed.

After operation vision improved to $\frac{6}{18}$ left and $\frac{6}{9}$ right; and there was return of vision in both temporal fields.

Discussion.—Dr. L. R. YEALLAND said that the surgeon was to be congratulated on the marvellous result. He (Dr. Yealland) thought that a lesion situated in front of the chiasma would produce the same effects on the visual fields as a lesion behind the chiasma; because it contained the nasal neurons coming from both retinæ.

Mr. HENDERSON (in reply) said that a tumour rising behind the chiasma very often produced a bilateral central scotoma rather than a bitemporal hemianopia.

Myasthenia Gravis: A Case in which Fatigue of the Forearm Muscles could induce Paralysis of the Extra-ocular Muscles.—MARY B. WALKER, M.D.

It is well known that in myasthenia gravis, weakness throughout the body develops if one group of muscles is exercised. The demonstration shows that during activity, myasthenic muscles liberate a chemical agent which passes into the blood-stream and blocks neuromuscular transmission at the motor end-plates of skeletal muscle elsewhere. The nature of this "curarizing" agent is at the moment unknown. It is suggested that the abnormal formation or imperfect destruction of this agent may be the cause of the weakness and fatigue of myasthenia gravis.

Evidence in support of this view was obtained in a case of severe generalized myasthenia gravis, in which the left eyelid, when not under the influence of prostigmin, droops so that the whole of the iris is covered. At a time when the effect of prostigmin is wearing off, the circulation is cut off in both arms by inflating sphygmomanometer cuffs to 200 mm. Hg. The forearms are then pronated and supinated until they are tired; this usually takes over a minute. No increase in the droop of the eyelid takes place at this stage. The pressure in the cuffs is then released. After a latent period of a minute and a half increased droop develops. In two minutes there is a very great increase in weakness of the muscles generally. The pressure has been maintained for varying periods after the pronation and supination have ceased, with the same results.

Discussion.—Dr. E. A. CARMICHAEL said that this was a most important demonstration if the fact was accepted that the succeeding weakness was caused by some substance which had been manufactured in the muscles exercised and was now circulating through the system. Did Dr. Walker think that this substance was peculiar to myasthenia or was known to occur in or to be manufactured by healthy individuals who exercised the muscles? It had been shown by physiologists that normal muscle, when fatigued, produced a substance which had a curarizing effect on muscles.

Dr. WALKER (in reply) said she thought it quite probable that the substance occurred in normal individuals.

Dr. MILLS said that he had been interested in the latent interval which occurred between the stoppage of the voluntary movements and the end of the four minutes during which the cuff was applied. He wondered what would happen if the circulation were cut off without any movement being carried out.

Dr. WALKER said that the release of the circulation was delayed for four minutes to show that the delay in the onset of increased weakness was due to the circulation being cut off and not to the latent period of one and a half minutes which occurred whether the circulation was cut off or not.

When the forearms were exercised without the circulation being cut off the droop in the eyelid began to increase after one and a half minutes' exercise, and continued to increase for two minutes after the exercise had been stopped. The forearms tired much less readily and the weakness of the other muscles was much less than when the circulation was cut off. The effect of cutting off the circulation for a period without exercise had not been observed.

Dr. DENNY-BROWN said that there was a difference between the disturbance indicated in this experiment and that which was supposed to occur according to the theory that myasthenia was due to an abnormal accumulation of fatigue products. The paralysis of myasthenia was something rather different from fatigue. In the case of a normal person exercise of a muscle below a cuff constricting the circulation was painful, but the failure of muscular contraction in myasthenia was not painful. This seemed to argue against the accumulation of fatigue products in myasthenia, yet Dr. Walker's experiment appeared to indicate that something had passed into the general circulation and could paralyse other muscles.

Dr. CARMICHAEL said that he was impressed by the dramatic way in which the patient had improved even during the few minutes since the experiment terminated and prostigmin had been administered.

Section of Medicine

President—H. L. TIDY, M.D.

[*February* 22, 1938]

DISCUSSION ON MINERAL SALTS IN THERAPY

Dr. R. A. McCance: The subject of mineral salts in therapy is such a general one that the major part of this discussion will have to be limited to certain of its aspects. I propose in the limited time at my disposal to try to give an account of what I conceive to be the rationale underlying treatment with sodium chloride.

To appreciate and understand sodium therapy it is essential to remember that the metabolism of this element is closely tied up with the metabolism of water. About 60% of the body is water. Roughly two-thirds of the body water is in the body cells. The remaining one-third is in the plasma, lymph, cerebrospinal fluid, and intercellular spaces, the whole of these being conveniently termed the "extracellular fluids". Recent work strongly suggests that the osmotic pressure of the cellular fluids is always equal to the osmotic pressure of the extracellular fluids. If we accept this, it follows at once that if for any reason the osmotic pressure of the extracellular fluids is altered, a corresponding alteration will at once take place in the osmotic pressure of the cellular fluids. It has also been shown, and about this there is no doubt whatever, that whereas the bulk of the cellular osmotic pressure is due to potassium salts, that of the extracellular fluids is due to sodium salts, and that on the whole the cellular membranes are freely permeable to water but not to sodium and potassium, or indeed to the other metallic radicals. There are, however, certain exceptions to these generalizations. There must be times during the metabolic life of all cells when their membranes are permeable to potassium, and indeed to other metallic radicals. If there were not it is difficult, for instance, to see how they could grow. It is well known, moreover, that the red blood-cells of certain animals, but not of man, contain sodium rather than potassium salts, and recent work has tended to show that *in vivo* the membrane of the red blood-cell is probably slowly permeable to basic ions. The red blood-cell, however, cannot be regarded as a typical body cell. For example, it has no nucleus and, unlike other cells, it contains large quantities of chlorides, so that reactions demonstrated to take place between the plasma and the red blood-cell should not be assumed to be taking place between the plasma and the other cells of the body until they have been definitely proved to do so.

Forced removal of water from the body (if such a procedure were possible without the simultaneous removal of sodium ions) or a reduction of the water intake to a minimum, produces a state of general bodily dehydration in which the intra- and extracellular fluids suffer, and probably to the same extent. The volumes of both fall and the osmotic pressures of both rise. The blood-plasma takes part in the general fall in the volume of extracellular fluids as demonstrated by a rise in the percentage of hæmoglobin and plasma proteins. This is a state of true dehydration, in which the

whole body is suffering from a shortage of water. It may be met with after any surgical operation on the stomach which prevents the patient taking fluid by mouth, and it is easily induced experimentally. It is quite distinct from shock and requires quite different treatment. Secondary changes supervene if the water deprivation becomes at all severe, for the reduction in the volume of the extracellular fluids—particularly the blood and lymph—prevents the normal exchange of metabolites between the blood and the tissues. The functional capacity of the kidneys is reduced by the diminished blood volume and by the fall in blood-pressure if this takes place. This state of generalized dehydration can be completely cured by the administration of water alone. It is unnecessary to give saline and to do so would be a mistake.

Forced removal of sodium from the body without any deprivation of water leads to a totally different picture. Deprived of some of its sodium, the body is faced with two alternatives or a compromise. Firstly, it may excrete the water with which the sodium was associated and so maintain the osmotic pressure of its extracellular fluids, and of the body generally, *in statu quo*, at the expense of a corresponding reduction in the volume of the extracellular fluids. Secondly, the body can maintain the volume of its extracellular fluids *in statu quo* and allow the osmotic pressure to fall. The rabbit sometimes does this. The moment the osmotic pressure of the extracellular fluids begins to fall, the osmotic pressure of the cells probably begins to fall also, and since the cell membranes are impermeable to sodium and potassium, the osmotic pressure of the cells can only fall by the cells taking up water. Thirdly, the body can compromise between a reduction in the volume of its extracellular fluids and a reduction in their osmotic pressure. This is what happens in man and, it would seem, in most animals. In the last condition, namely in the compromise, we may have a picture of severe reduction in the volume of the extracellular fluids with signs of anhydræmia, viz. a rise in the percentage of hæmoglobin and plasma proteins: yet combined with this we have a lowered serum sodium and probably a state of overhydration of the cells. The reduction in blood volume has the effect already described, and the exchanges of metabolites between the cells and the plasma is further interfered with in a sodium deficiency by the swelling of the cells, which compress the lymphatic vessels and tissue spaces. In addition to these effects the kidney, for some reason at present unexplained, cannot produce a copious diuresis following the ingestion of a large quantity of water. The syndrome which I have just described can only be cured by the administration of salt. The administration of water alone is of no avail. It is therefore important that saline should be given to all patients who have lost salt, from sweating, vomiting, diarrhœa, or one of the rarer causes. It does not matter how the saline is given. It can be given by mouth if the patient can tolerate it, or it can be given by rectum, for sodium salts are absorbed by the large intestine. The most effective method, however, is to give the saline intravenously.

When the body is unable, for any reason, to excrete sodium salts, their administration in the food or in any other form inevitably leads to an increase in the volume of the extracellular fluids and, ultimately, to œdema. The converse is also true for œdema, whatever its ætiology, is necessarily associated with excessive amounts of sodium in the body and an increased volume of the extracellular fluids. The most effective treatment is to remove the salt from the body, for if this is done the water which was associated with the salt will be excreted by the kidney. Indeed, if a salt-free diet is used to reduce œdema, it is unnecessary to restrict the water intake. Diuretin appears to act by forcing the kidney to excrete sodium chloride and its success in the treatment of œdema depends upon this. Some animals can be made salt-deficient and killed by large doses of diuretin. The treatment of œdema always demands caution. Some patients with œdema have an abnormally large blood volume; others have not. It may not be possible to remove the œdema without a very material reduction in the blood volume, and this may be so great that signs of anhydræmia

supervene. The French literature contains numerous references to this danger and many descriptions of cases.

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Dr. R. S. Aitken: My contribution will be restricted to the use of potassium in the treatment of family periodic paralysis. A male patient, aged 21, who had suffered from typical attacks of this rare condition since the age of 14, was admitted in May 1935 to St. Alfege's Hospital, and came under Dr. Mary Walker's care. His attacks of paralysis occurred typically at night, and he thought they were specially apt to occur after unusual exertion or a heavy evening meal, and especially a heavy consumption of sweets. They lasted from eight to forty-eight hours, and Dr. Walker found that they could be induced at will by giving him 150–225 grm. of glucose in the evening. The possible mechanism of these attacks was discussed with Dr. E. N. Allott, who suggested that an electrolyte disturbance would most readily explain the rapidity with which the paralysis began and ended, and that a disturbance involving those electrolytes known to be connected with sugar metabolism (namely lactic acid, phosphate, and potassium) might first be looked for. He undertook a complete electrolyte analysis of the patient's blood during and after an induced attack, and found the only significant alteration to be in the serum potassium concentration, which was reduced to half the normal during the attack.

The patient next came under observation in St. Leonard's Hospital, in 1936, when this striking fall in serum potassium was again demonstrated, both in a spontaneous attack and in an induced one. It was also found that, after 12 grm. of potassium chloride had been given by mouth, the paralysis passed off within an hour and the patient was apparently restored to normal. He then left the hospital, but was admitted to Hammersmith Hospital in 1937, where he remained long enough for a series of further observations to be made. Nocturnal attacks were again induced by giving glucose, and terminated by giving potassium. Insulin (30 units) given subcutaneously when the patient was fasting induced a mild attack in the daytime, and the administration of 10 units of insulin and 25 grm. of sugar, the latter by mouth, every hour for about five hours, regularly brought on a severe attack; the serum potassium fell steadily from its normal level of 16–20 mgm. per 100 c.c. and paralysis supervened when it approached 10 mgm. per 100 c.c.

Control observations on normal subjects showed that a moderate fall of serum potassium, without muscular weakness, could be produced by giving 250 grm. glucose by mouth, by injecting insulin, or by simultaneous glucose and insulin, but all these procedures produced in the patient a much greater fall. Adrenaline will also lower the serum potassium, both in normal people and in patients with periodic paralysis, and in the latter it sometimes induces attacks. There are several instances on record in which serum-potassium values below 10 mgm. per 100 c.c. have been found in patients not affected by periodic paralysis; they showed no muscular weakness.

It is therefore concluded that in the patient on whom the above observations were made two abnormalities exist: an undue lability of the serum potassium, which fluctuates widely with alterations in carbohydrate transport, and an abnormal sensitivity of the neuromuscular apparatus to low serum potassium concentrations, which inhibit contraction. The mechanism of each of these abnormalities is still obscure.

The value of potassium in the treatment and prevention of attacks—which has been firmly established by these observations—is not an altogether new discovery. Singer and Goodbody (1901), describing a case of periodic paralysis from the National

Hospital, Queen Square, attributed the attack to an accumulation in the body of some toxic substance which was susceptible of excretion in the urine. They recommended diuretic treatment with digitalis and potassium citrate or acetate, but claimed no great success from it. Mitchell, Edsall, and Flexner (1902) in America, recorded three cases, in the first of which the patient, "an intelligent, well-educated woman, had made for herself the interesting observation that citrate of potash in good-sized doses would cut short an attack". In one or other of the three cases, potassium citrate, potassium bromide, and potassium chlorate, were all observed to shorten attacks, though potassium carbonate, as well as sodium bicarbonate, was said to be without effect. Holzapple (1905) had observed for twenty years an American family which included over a dozen subjects of this disease. Believing the attacks to be due to a vasomotor spasm of the anterior spinal artery, he tried large doses of bromide of potassium and he produced good evidence that a half-drachm dose, repeated in one or two hours, was often successful in aborting impending attacks. Willoughby Gardner (1913), who described an example of the condition from Shropshire, drew up an elaborate scheme of treatment which included both Holzapple's and Singer and Goodbody's prescriptions, and by means of it succeeded in keeping his patient's attacks in abeyance for two years.

In the light of Allott's recent discovery it seems likely that all those older physicians were making sound observations, but that the benefit which some of them were variously attributing to citrate, acetate, chlorate, or bromide, was really due to the common ion, potassium.

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Dr. C. L. Cope: I want, in the few minutes at my disposal, to call attention to another aspect of the commoner mineral salts, and that is their possible toxic effects.

First of all, at the risk of sounding platitudinous, I should like to stress the fact that all mineral salts consist inevitably of a basic and an acidic radical bound together. Once the salt is taken into the body, these two radicals become, from the pharmacological point of view, separate, and exert their own actions quite independently. This duality of pharmacological action endows mineral salt therapy with a peculiarity of its own. It is quite inescapable and has always to be reckoned with, for no metallic radical, with rare exceptions, can be administered without being accompanied by some acidic radical. Even sodium, to which our first speaker has referred, cannot be administered save in association with chlorine as saline, or with carbonic acid as bicarbonate, or in some other salt. It behoves us, therefore, when administering any metal, to make sure that the associated acid radical has no harmful effects. And conversely, when an acidic radical is to be administered, the basic radical to which it is linked must be chosen because of its innocuous nature.

This may seem to be an obvious truth, but I am encouraged to express it in this form by the memory of a case seen some years ago.

This was in a man ill with some form of hæmorrhagic blood disease, the precise nature of which slips my memory, and is in any case immaterial. The physician-in-charge was anxious to treat the patient with large doses of calcium. He had learned, quite correctly, that the most readily absorbed salt of calcium is the chloride, and accordingly administered calcium chloride to his patient in considerable amount. He did not adequately appreciate, however, that most of the calcium would be re-excreted into the bowel, leaving behind in the body a constantly accumulating excess of chloride, or what for all ordinary purposes was hydrochloric acid. The result was

that the patient developed a severe acidosis which was by no means an intended result, and which, in fact, made him considerably worse.

In this case the desire was to administer calcium, but the wrong acidic radical was chosen to accompany it. If the lactate had been used, of course, all would have been well, for lactic acid, unlike hydrochloric acid, would not have accumulated in the blood, but would have been destroyed as fast as it was set free, and so no acidosis would have occurred.

It may be that mistakes of this type are very infrequent, but it is perhaps well to realize that the reason they do not occur much more often is the extreme efficiency of the normal organs of excretion, especially the kidney. The absorption of any salt tends to upset the normal ionic balance of the body fluids. The kidney at once attempts to correct the upset, and its powers in this direction are so great that very large quantities of many inorganic salts may be ingested without harmful result, provided only that the kidneys are functioning normally.

It is true that even the healthy kidney fails occasionally to cope with the ionic disturbances of body fluids produced by the treatments of the physician, but such cases are rare. The normal kidney appears, for instance, to be incapable of distinguishing between chloride and bromide, with the result that in prolonged bromide therapy, the bromide may be permitted to accumulate in the blood-stream, the normal chloride being excreted in its stead. Attention has recently been drawn to the undesirable symptoms which may accompany such an accumulation.

But it is when the excretory mechanisms of the body are impaired that trouble is most likely to occur during mineral salt therapy, and particularly so with the type of salt which is given as a rule in large quantities. And it must be remembered that renal function is frequently impaired in many conditions besides that group linked together clinically as nephritis. It is damaged in diabetic coma, in dehydration and salt deprivation, and in some forms of alkalosis.

Dr. McCance has pointed out how excess of sodium in the body may lead to œdema, even in normal persons. In pre-insulin and early insulin days much sodium bicarbonate was administered in an effort to combat the acidosis. Cases of generalized œdema appear to have been more frequent among diabetics then than they are now, and the suggestion that this œdema was due to the giving of too much sodium was made and has, so far as I am aware, never been disproved.

We have heard, too, of the startling value of potassium salts in therapy to-night, but potassium also has its toxic action. Some years ago Blum (1920), in France, was impressed with the beneficial effects of restricting sodium chloride in the dietary intake of patients with œdematous nephritis. Partly for experimental reasons, and partly also in an effort to make the sodium-poor diet more appetizing, he attempted to replace the sodium by potassium chloride in the diet, with the result that he had numerous cases of potassium poisoning among his patients. Colic and diarrhœa were frequent even after relatively small doses, and 20 grm. in the day was sometimes sufficient to cause circulatory collapse with cyanosis and fall of blood-pressure. Others, too, have reported similar toxic effects after giving potassium chloride to nephritic patients.

Now at the present time, potassium salts, in the form of citrate are being given in large quantities to persons suffering from pyelitis. The intention is to render the urine alkaline ; the role of the potassium is incidental. If in such persons there is severe renal functional damage, as may well occur from associated pyelonephritis or from other cause, then the urine will not be so easily made alkaline as if the kidney were normal. In these circumstances there is a temptation to increase the dose of potassium citrate, and if this is done the conditions would seem to be very suitable for the development of potassium poisoning. I have not actually heard of potassium poisoning from this cause, but all danger could be avoided by the use of sodium citrate.

The use of either of these salts in conditions of renal damage is liable to lead to another untoward result, of which I have seen a good example. These citrates act by virtue of the fact that the acidic radical is destroyed in the body, leaving behind an excess of the alkaline metallic ion. A tendency to alkalosis is thus produced, and the alkaline urine is merely an outward sign of the efforts of the kidney to remove this alkalosis. If the kidney is damaged and unable to produce a sufficiently alkaline urine the alkalosis may remain unrelieved. If then the physician, in a more strenuous endeavour to force the urine to become alkaline, increases the dose of potassium citrate, the alkalosis may become intensified to an unpleasant degree.

This is apparently what occurred in a case which I have in mind. A young girl suffering from pyelitis was treated with potassium citrate, the dose being increased to about 20 grm. a day, in an unsuccessful effort to make the urine alkaline. After ten days on this dose she became lethargic, felt very weak, vomited, and finally became definitely drowsy. The blood alkali reserve was raised to 80 volumes %, and the blood urea, which had been practically normal, was now 318 mgm.%. Twenty days after the withdrawal of all further citrates the blood urea had fallen to 20 mgm.%, and the alkali reserve was normal. Her mentality was again bright and cheerful, although the pyelitis was still present. Throughout, the urine had remained acid—or, at most, neutral—in reaction. It is now well recognized that alkalosis can co-exist with an acid or neutral urine. This was, I believe, an example of the untoward results of giving mineral salts in excess of the amounts with which the damaged kidney can deal.

Now let us consider another supposedly innocuous substance—magnesium, in its salts. Magnesium is perhaps given in largest amounts as the sulphate for its effect as a purgative. When a full purgative dose of magnesium is given to a person with healthy kidneys, some is absorbed into the blood-stream, but it is excreted so rapidly, largely by the kidneys, that no appreciable rise in the magnesium concentration of the blood occurs. But in persons with severely damaged renal function the result is very different. It has been investigated carefully by Hirschfelder in America (1934). The normal level of the magnesium in the plasma is very constant at about 2 mgm.%. Even in severe nitrogen retention it does not as a rule rise much above 3 mgm.%. But if to a severe nephritic a full purgative dose of magnesium sulphate be given, the plasma magnesium rises very considerably, even to 10 or 15 mgm.%. Such a concentration is quite sufficient to cause drowsiness or even a light degree of coma. A plasma concentration of 17 mgm. is generally considered to produce full coma, and two-thirds of this concentration can be produced in the nephritic by a purgative dose of magnesium sulphate given by mouth. One wonders how often coma is precipitated in cases of uræmia by a well-meant dose of Epsom salts.

Arising from these observations comes an interesting suggestion which was made originally by Hirschfelder. It has been found that an animal with even a slightly raised magnesium in the blood is very much more sensitive than normal to ordinary therapeutic doses of morphia. Now Epsom salts was Sir William Osler's favourite purgative at the Johns Hopkins Hospital. It is, therefore, probable that his cases of nephritis often had a raised plasma magnesium. It was he who stressed so strongly that to nephritics morphia should always be given with great caution. Again one wonders to what extent this well-recognized sensitivity of nephritics to morphia is due to the use of magnesium sulphate as a purgative.

Magnesium is used in large quantities in another field of therapy. As the oxide or carbonate it forms an important constituent of the alkali used in the treatment of gastric and pyloric ulcers. In normal persons with healthy kidneys this large and continued ingestion of magnesium has no untoward effects. In a series of such persons whom we have examined there was no appreciable accumulation in the blood of any. But occasionally some upset occurs in persons on alkali therapy which results in a profound disturbance of kidney function. The precise nature of this upset is

not understood, but it is called alkali poisoning or gastric alkalosis. Several writers during the last few years have called attention to this condition. From the present point of view the importance of this alkali poisoning lies in the fact that it is associated for the time being with a severely damaged kidney function. The blood urea is very considerably raised, and functionally the condition is equivalent to an advanced nephritis.

We have seen that in the advanced nephritic magnesium salts may cause a serious rise in the magnesium concentration of the plasma, and the same seems to happen in cases of alkali poisoning. I have had the opportunity to examine a number of these cases and in all there has been a definite rise in the plasma magnesium level. In some it exceeds three times the normal figure. Now important clinical features of these cases are depression, mental lassitude, irritability, and finally definite drowsiness. Such symptoms are precisely those to be expected from a chronic mild magnesium poisoning, and it seems not improbable that magnesium retention is at any rate one of the factors involved in producing the peculiar symptomatology of this condition. Cases of alkali poisoning are from time to time diagnosed in the wards of the general hospitals, but vast amounts of these stomach powders are taken by sufferers from various types of indigestion, many of whom are not under medical supervision. It seems almost certain that some cases escape detection, and the patients persist for long periods in a state of mental depression, the depression being due to the continued ingestion of alkalies. I have myself encountered one such case, in a man who finally consulted his medical adviser because of several months' chronic irritability and depression and the fact that he kept quarrelling with his wife. The doctor diagnosed neurasthenia and advised a holiday, which he took; this, however, brought about no improvement, and he finally entered hospital, where alkali poisoning was diagnosed. The blood urea and alkali reserve were both very much raised, and the plasma magnesium was also high. The patient was persuaded to give up taking alkalies, and had an uneventful recovery, being restored to a normal outlook on life.

That this type of alkali poisoning is associated with a severe degree of alkalosis is now well recognized. This alkalosis is presumably the result of administering alkali in greater amount than the damaged kidney can deal with. What precisely brings about this damage to the renal function is not known. But if the kidney is functioning normally no such tendency to alkalosis is shown. Another example of the fact that it is the efficiency of the kidney, in the main, which permits such latitude in our use of mineral salts in therapeutics. A still further example is the response of such alkalotics to ammonium chloride. Cooke (1933) has pointed out that ammonium chloride must be given with great caution to such patients when we are attempting to reduce the degree of alkalosis, as there is great danger of the condition going over rapidly into acidosis. The kidney is no longer able to aid the clinician's efforts.

Finally, a word about calcium, of which alkaline stomach powders contain a considerable amount. By the great majority of individuals this calcium is satisfactorily dealt with. In a series of patients with gastric ulcer who were under treatment with alkalies containing calcium carbonate I found no signs of retention in the blood-stream. But when alkali poisoning develops, with its alkalosis and severe functional renal damage, the situation becomes quite different. In such cases the calcium of the blood is greatly increased. I have myself found values as high as 16 or 17 mgm.% instead of the normal 10 mgm. Such values would be considered high even in hyperparathyroidism. I am not prepared to say that such high blood-plasma calcium levels do definite harm. But there are several points which make one wonder. It is almost certain that a small proportion of persons taking alkaline powders for stomach complaints do at times suffer from raised blood-calcium. We know that a chronic form of alkali poisoning may occur and may remain unrecognized for some time. Now Albright (1934) and his associates have described several types of

renal lesion which occur in association with the chronic hypercalcæmia of hyperparathyroidism. Similar renal lesions occur from excessive dosage with vitamin D. And a few years ago lesions of this type were described by Cooke, in a series of patients dying from pyloric obstruction. All these patients gave a history of gastric trouble previously and all had probably been taking alkaline powders containing calcium.

The possibility that the prolonged taking of large amounts of calcium in stomach powders may in time have a deleterious effect on the kidney in some cases seems, therefore, at least worthy of consideration.

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Section of Surgery

President—G. GREY TURNER, M.S.

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DISCUSSION ON THE TREATMENT OF ACUTE STREPTOCOCCAL INFECTIONS

Dr. S. C. Dyke: Acute infections due to non-hæmolytic streptococci are not common and are, for the most part, neither severe nor dangerous to life. The hæmolytic streptococci, on the other hand, are among the most dangerous of all infecting agents. The treatment of infections due to non-hæmolytic streptococci remains much where it has been for the last century; the treatment of infections due to the hæmolytic streptococci has, however, lately undergone a remarkable change owing to the introduction into therapeutics of the compounds of the sulphanilamide group. Two years ago the hæmolytic streptococcus successfully maintained pride of place as one of the most dangerous and most dreaded of all the infecting agents to which human beings are susceptible; the therapeutic armamentarium held no effective weapon against it, and treatment resolved itself into the employment of the time-honoured measures of rest and heat. Rest and heat remain as important as ever, but in the sulphanilamide compounds the practitioner of medicine now for the first time possesses the means of making active and effective onslaught on the organisms.

Some obscurity hangs about the history of the discovery of the bactericidal effect of the sulphanilamide compounds. So far as it has resulted from chemotherapeutic research it may be claimed as a triumph for the scientific method. Domargk, however, who conducted the original investigations, was working on the antibacterial action of di-azo dyes, and the first preparation put on to the market was in fact a red dye. It remained for Buttle and his co-workers in this country, and the Tréfouels and their co-workers in France, to show that before the dye can be effective the di-azo linkage has to be split, and that the essential compound is of the parabenzene-sulphonamide formula. Various drugs of this formula with the amino radical in the para position, and containing a sulphone group, were found to protect mice against a number of organisms, but to have a particularly powerful action against the hæmolytic streptococcus.

The value of these compounds of the sulphanilamide class in the clinical treatment of hæmolytic streptococcal infections is now attested by a vast cloud of witnesses. It is in the commonest and the most fatal variety of this type of infection—that associated with childbirth—that it has been most clearly and conclusively demonstrated. The statistics produced by Colebrook and his co-workers at Queen Charlotte's Hospital leave no room for doubt as to the value of the sulphanilamide compounds in the treatment of puerperal septicæmia. For cellulitis, lymphangitis, and other acute hæmolytic streptococcal infections, usually regarded as surgical, no comparable array of data is available.

Although no important series of cases exists to demonstrate the efficacy of the sulphanilamides in surgical practice, that efficiency does not remain in doubt. Everyone who has come in contact with cases of acute hæmolytic streptococcal infections has evidence of it. Unhappy experience in the past has made us all too well acquainted with the type of case in which a fatal issue was inevitable. Being hopeless, such cases in the past fell almost automatically to the lot of the hospital pathologist, who was invited to do his worst with sera vaccines or anything else he fancied. Two outstanding examples of such hopeless cases fell to my lot at the outset of the sulphanilamide era. The first was in a child aged 11 admitted with high temperature and swelling of several joints; hæmolytic streptococci were isolated from pus aspirated from the knee-joint and from the blood-stream. On all previous experience the outlook was hopeless. Treatment by a combination of sulphanilamide compounds

both orally and parenterally was, however, followed by fall of the temperature and recovery ; the inflamed joints subsided after simple aspiration. The second case was that of a diabetic girl aged 26 admitted almost in coma and with a large and rapidly spreading phlegmon of the right arm. Clinically the infection bore all the signs of being due to a hæmolytic streptococcus, and treatment with sulphanilamide was initiated. The temperature fell, the spread of the phlegmon ceased, and ultimately pus formed in two places ; this was liberated and gave a growth of a hæmolytic streptococcus.

The efficacy of the sulphanilamides in hæmolytic streptococcal infections is now beyond doubt. The problems now awaiting solution are the best type of compound to use and the method of employment.

The first of these compounds to be put on the market was a diaze compound containing two linked benzene rings. It is sparingly soluble in water but is quickly absorbed from the intestinal tract and diffuses throughout the whole system with the utmost readiness. It is therefore eminently suitable for oral administration. That a drug, and in particular a systemic antiseptic, must be more effective if administered parenterally than by the simple oral route is almost an article of faith in present-day medicine and, moved by the desire to produce a soluble preparation suitable for parenteral injection or to reduce toxicity or merely with the desire to be different, the commercial drug houses at once busied themselves with the introduction of benzyl, phenyl, and other radicals into the simple formula.

The only cases calling for parenteral treatment are those in which for some reason, such as persistent vomiting, the oral route is not available. The oral route should be used whenever possible. Of the preparations for oral use the efficacy of the paramino-benzene-sulphonamide is now proven. The introduction of a benzyl radical is said to lessen toxicity ; this may or may not be so—in any case the benzyl preparation appears to be as effective as the formula lacking this radical. Being insoluble in water, these compounds must be administered as tablets or in the form of powder ; anyone who has been under the necessity of taking them is in a position to understand the full meaning of the phrase " dust and ashes in the mouth " but, bearing in mind recent American experience of the catastrophic results attending attempts to produce a palatable liquid preparation, this may be regarded as a minor inconvenience. For parenteral use various preparations of highly complex formula are available. All these, before they become effective, must be split in the body into the simpler amino-benzene-sulphonamide. How long this splitting takes is not known, but there is no reason to suppose that the effective compound is made available any more rapidly when administered parenterally in the form of a compound from which it has to be liberated than if given by mouth. Combination of the parenteral with the oral administration appears to possess no advantages over the simple oral route.

Early in the history of the use of the sulphanilamide compounds it became evident that they were capable of giving rise to untoward symptoms of various sorts ; this has led to a search for less toxic compounds which up to the present has not been particularly successful. The most striking of these disturbances and the first to attract attention were sulph- or met-hæmoglobinæmia or a combination of the two. Most people who have used the drug have experience of the rapid development by the patient of a bluish-grey cyanosis which when first seen is distinctly alarming ; in spite of their unpleasant colour the general condition of the patients is for the most part not deleteriously affected. Neither sulph- nor met-hæmoglobin are in themselves harmful ; their only significance is that, when formed, they prevent a certain proportion of the hæmoglobin from carrying out its normal function. The amount of hæmoglobin withdrawn from service is as a rule negligible ; where, however, there has been anæmia before commencement of treatment the amount withdrawn may be sufficient to give rise to oxygen deficiency. This can easily be combated by infusion of blood and constitutes no contra-indication to the employment of sulphanilamide.

The occurrence of sulphæmoglobinæmia is due, as shown by Archer and Discombe, to the catalytic action of the drug upon the sulphuretted hydrogen present in the bowels, with consequent liberation of nascent sulphur. Hydrogen sulphide is present in the bowels in significant quantities only in face of grossly abnormal fermentation. The commonest cause for this is purgation; if aperients of all sorts are withheld during the exhibition of the drug, sulphæmoglobin formation is usually minimal and insufficient to give rise to any change in the colour of the patient. After withdrawal of the drug the sulphæmoglobin rapidly disappears from the blood.

Other manifestations which may occur in the course of treatment fall more under the head of idiosyncrasy. Of these perhaps the most disconcerting is pyrexia. This usually appears from a week to ten days from the commencement of the administration of the drug; it is only noticeable in those cases in which the initial temperature has already fallen and all appears to be going well. Then one day the chart is found to show a rising temperature; on the second day it may be up to 103°; there may be some malaise but there is no marked deterioration in the general condition. In spite of this the temperature chart may be taken as evidence of renewed activity of the infection and dosage with the drug renewed if it has been dropped, or increased. The temperature usually falls within three or four days. This manifestation is only of importance on account of the alarm and despondency to which it may give rise.

With the temperature there may be a rash; this is the most sensational manifestation of idiosyncrasy to the drug. Usually it is morbiliform, though I have once seen a scarlatiniform rash. It is readily distinguished from measles by the fact that it is more characteristic than any measles rash ever is, and that it is unaccompanied by coryza or conjunctivitis. It may cover the whole of the face, trunk, and limbs, and in severe cases is very irritating; there may be considerable puffiness of the face, particularly of the eyelids. The rash rapidly disappears on withdrawal of the drug. Certain patients experience nausea after each dose of the drug; this, however, constitutes no indication for cessation of the treatment.

The drug is undoubtedly capable of giving rise to very unpleasant symptoms, but its capacity to give rise to serious tissue damage appears to have been overestimated. Hawking, giving relatively enormous doses to cats, found the only significant effect to be that upon the central nervous system. In view of its supposed toxicity it has been customary to withhold the drug when there is any question of renal or hepatic insufficiency, but there appears to be no good reason for this. My own experience with diabetics would lead me to believe that the drug may safely be exhibited even in face of the most generalized and severe metabolic disturbances.

The question of dosage remains unsettled, and it is probable that the huge doses used by some observers have in many cases been responsible for the embarrassing symptoms. My own experience leads me to believe that the doses frequently used are unnecessarily large. I have found a dose of 4 grm. on the first day of treatment, and thereafter of 3 grm. daily, to be ample in all cases; something in this region I believe to be the optimum.

After three days of such dosage the patient, if capable of improvement, will be showing definite signs of it; otherwise he will be dead or moribund. At the end of a week's course there will be marked improvement; hæmolytic streptococci may still be present in the lesion but they will be under control. The mere persistence of the organisms in the lesion is no indication for persistence with the drug. The aim of the treatment is not to destroy all hæmolytic streptococci in the tissues but to sway the tide of battle in favour of the natural bactericidal forces of the body; once they have got the upper hand they can safely be left to assume complete mastery. In this, as in all other conditions, the patient, and not a laboratory finding, should be the object of treatment.

The mode of action of sulphanilamide remains obscure; in aqueous solution the sparingly soluble paraminobenzene-sulphonamide and its more soluble derivatives are

both only very slightly antiseptic. In blood, *in vitro*, they are much more effective, but they only show their maximum action in the presence of the leucocytes. Finkelstein-Sayliss and his co-workers have produced evidence that the sulphanilamide drugs are greedily absorbed by the fatty envelopes of the hæmolytic streptococci; it is reasonable to suppose that this has something to do with their action on the organisms. These workers have further shown that the sulphanilamide compounds have a stimulating action upon the reticulo-endothelial system. It seems probable that the bactericidal action of the compounds is due to a complex of factors involving both the immunity reaction of the host and the resistance of the organisms. The findings of Buttle indicate that the leucocytes play an important part in destroying the organisms. They do not appear to be rendered more actively phagocytic, but under the action of the drug the organisms seem to become more susceptible to their embraces. Agranulocytosis has now been observed in a number of cases under sulphanilamide treatment, and such cases have all done badly; on the face of it it would appear that anything bringing about a leucocytosis should help the action of sulphanilamide, and I have no doubt that someone will shortly advocate injections of nuclein or pentnucleotide as an adjuvant to the treatment; I should not expect them to be of much assistance.

What is known of the mode of action of sulphanilamide lends no support to the view that it can be of any service as a local antiseptic. Various reports have appeared of its use by injection into the pleural sac, and by lavage of the spinal thecal canal in the case of hæmolytic streptococcal infections; the results give no reason to suppose that it can usefully be employed in this way. Nicholson, working on experimentally induced hæmolytic streptococcal infection of the pleura in rabbits, has recently reported that introduction of sulphanilamide into the pleural sac was without influence on the course of the infection. All the evidence goes to indicate that sulphanilamide is a systemic and not a local bactericidal agent; its action must be through the blood and tissues of the host, and it is most usefully administered by the route permitting of the most rapid diffusion throughout the system; this on the present evidence appears to be the oral.

In conclusion may I say that if in any case of hæmolytic streptococcal infection after ten days' suitable treatment with sulphanilamide the temperature remains raised and the condition is not improving, it probably means that, as a result of the arrest of the actively spreading infective process, localization with formation of pus has taken place. Then, and in no circumstances until then, is the time to consider the use of the surgeon's knife.

Mr. T. B. Layton said that because he disagreed with all the premises of the introducer he did not wish it to be thought that in his opinion sulphanilamide was of no value. He was not prepared to admit that the approach to the treatment of acute streptococcal infections was very different to-day from what it was two years ago. The approach remained the same. The difference lay in the fact that a drug had at last been discovered which seemed to kill the hæmolytic streptococcus in the blood-stream and thus gave a hope of saving lives in cases that had previously seemed hopeless. But he was not prepared to accept the statement that before its introduction we had no remedy that was specific and effective against the hæmolytic streptococcus. The remedy that we had had and still had was to remove the factory of organisms from which invasion of the blood-stream was arising and then to treat the patient with vast quantities of fluid and by careful nursing, which included, to a certain extent, that rest upon which Dr. Dyke had, quite rightly, laid such great stress. The reason why the success of this drug had been so great in the treatment of puerperal septicæmia and in that which arose from the pricked fingers of surgeons and pathologists was because these were the two outstanding clinical types of septicæmia in which the surgical removal of the factory of organisms was impossible.

He was by no means certain that sulphanilamide was a " specific " remedy against the hæmolytic streptococcus. All that was known at present was that it had the power to kill the organism in the blood ; it was yet to be proved that it had any effect upon the organism in the tissues. If it did not do so they were faced with the possibility that by giving the drug they might mask the symptomatology of an active infective lesion by abating the general symptoms while allowing the disease to progress locally. In reference to this he would point out that fully controlled clinical observations had been made on sulphanilamide and the hæmolytic streptococcus by other observers than Colebrook and his co-workers. Mitman and Hogarth had made a series of such observations at the Eastern Fever Hospital in scarlet fever with a view to finding out whether the giving of sulphanilamide had any influence upon the development of secondary complications in this disease. Their results, which they had put before the Section of Medicine,[1] showed that in this series of cases the administration of sulphanilamide had had " no significant effect upon the duration of the initial pyrexia, the initial toxæmia, or the incidence of complications ".[2]

He (Mr. Layton) thought that the surgeon must be allowed to develop some judgment as well as to exhibit his manual dexterity, and while he agreed that the surgical treatment of hæmolytic streptococcal infections under certain conditions and in certain areas of the body resolved itself into the evacuation of pus after it had become well localized and walled-off, yet there were sites within the body where the nearness of a lethal structure would result in the death of the patient in certain clinical types of infection before that localization had occurred. A good example of this anatomical relationship was that of the mastoid bone to the meningeal cavity. So tragic and so dramatic was the involvement of this last that he thought that in all circumstances it must be considered with the utmost gravity. Many, perhaps all, otologists had tried the injection of drugs and sera into the cavity, with uniform failure. It was but to be expected that in the early days of sulphanilamide this also should be put into the theca, for it was not then known that it acted as well when given by the mouth as it did when administered by other routes. He thought that in sulphanilamide they had at last that accessory treatment to surgery in fully developed cases of otitic meningitis that they had long been looking for ; but he doubted whether it would ever make mastoid surgery a thing of the past. Certainly it had not yet, and he, for one, would not take the responsibility of refraining from surgery in a case of meningitis in which he thought it possible to remove the factory of organisms in contact with the outer surface of the dura mater.

Miss Meave Kenny said that surgery had not been of much use in acute streptococcal infections of the puerperium. Even early drainage of the peritoneal cavity had left almost unchanged the very high mortality from generalized peritonitis. The use of sulphanilamide without any surgical measures had greatly changed the outlook in such cases.

Sulphanilamide appeared to prevent the extension of infection to the pelvic cellular tissues, a limitation of disease process reflected in the prompt fall of temperature and rapid convalescence of treated cases.

Early bacteriological investigation and adequate, which sometimes meant prolonged, administration of the drug, were the factors on which depended the success of the new therapy.

Professor J. B. Cleland said that in Adelaide the use of compounds of the sulphanilamide group had given favourable results in some cases of streptococcal infections. He asked what course should be followed when an accidental wound

[1] *Proceedings*, 1937, **31**, 158 (Joint Discussion : Sect. Med. with Sect. Therap., 10).

[2] *Brit. Med. J.*, 1937 (ii), 1160.

was inflicted during a post-mortem examination. Should the drug be administered forthwith or should it be withheld until there was evidence of infection at the site of the injury ?

An interesting case, showing why in some instances these compounds might fail, was that of a girl aged 16 who had recently died at the Adelaide Hospital. She had complained of a sore throat and of loss of energy and interest for a fortnight before admission. The tonsils were reddened but not enlarged, and the lower lip was swollen. The blood-count showed a leucopenia (2,500 leucocytes per c.mm. of which only 4·1% were polymorphonuclears). A hæmolytic streptococcus was grown from the blood-stream and *Staphylococcus albus* from a sore on the lip. Prontosil was given, about a week after admission, and apparently temporarily controlled the streptococcus in the blood-stream. Difficulty in swallowing, however, developed, with drowsiness, signs of pneumonia, and a high temperature, and the patient died nineteen days after admission. Post-mortem examination showed a sloughing œsophagitis, with masses of cocci and numerous fungal hyphæ, and patches of *S. aureus* pneumonia. *S. aureus* and a hæmolytic streptococcus were grown from blood within the heart. A small white infarct in the spleen showed numerous chains of streptococci, but none were detected in the adjacent living splenic tissue. In the dead tissue, beyond the influence of any bactericidal substances in the blood-stream, the streptococci had evidently multiplied freely. Such a focus would form a source of eventual reinfection supposing the streptococcal blood infection had been successfully overcome. The patient's death was attributed to the *S. aureus* pneumonia and the sloughing œsophagitis. The granulocytopenia was present before the prontosil had been administered, and the history suggested that this condition had facilitated the infections that were present rather than that an infection was primarily responsible for the diminution in polymorphonuclear cells.

Dr. G. A. H. Buttle: In experimental staphylococcal infections in mice some degree of therapeutic effect is obtainable by administration of sulphanilamide, although this effect is not nearly so great as that obtained in hæmolytic streptococcal infections. It seems likely that there is some variation in the response of different strains of staphylococci to sulphanilamide so that it might be worth while to try large doses in clinical cases which would be expected to be fatal.

At the London Fever Hospital the number of operations for mastoiditis in the scarlet fever wards has been greatly reduced since Mr. R. Massingham began—six months ago—to administer sulphanilamide in all cases in which there was a discharge from the ear. The adult dose was 4 grm. and the dose for children was correspondingly smaller.

The President said that the question of the prophylaxis of streptococcal infections should not be overlooked. In recent years he had been disappointed at the amount of severe sepsis which he had seen after accidental wounds. He thought that probably some part of this was due to the neglect of antiseptics in the management of compound injuries. It was all very well to excise wounds, using an aseptic technique, but it was not always possible to get rid of all the damaged—and probably infected—tissue, and it was a mistake to endeavour to do without antiseptics altogether.

A considerable amount of nonsense had been talked about the damage done to the tissues by antiseptics, which was as nothing compared with the damage if living organisms were left behind. It was just in the treatment of this sort of injury that bipp, introduced by Professor Rutherford Morison, had proved so valuable. He (the speaker), however, did not like a greasy preparation, and preferred to mix the bipp powder into a paste with 1 : 40 carbolic, or with plain water. Made in this way, it could easily be spread on the tissues, and would stay where put.

United Services Section

President—Lieutenant-General W. P. MacArthur, C.B., D.S.O.

[*March* 14, 1938]

Coliform Bacillus Infections of the Male Urinary Tract

By Group-Captain A. F. Rook, O.B.E., M.R.C.P., D.P.H., R.A.F.

A medical officer working on the clinical side in the Services has certain advantages over most of his civilian colleagues. One of these is that he is dealing with a known and only slightly varying population of appreciable size. It is a picked population, and therefore caution is necessary in attempting to draw conclusions from the disease incidence. With certain diseases the incidence appears to be similar to that occurring in the general male population. He is thus in a position to work out fairly accurate morbidity rates, as nearly all patients in the known population are eventually admitted to Service hospitals. A second advantage is that the majority of patients are seen early and the records of all cases, slight or severe, are available for study. It is thus possible to obtain an unbiased view of the usual severity of a disease and not one distorted by seeing only the more severe cases. Another advantage, although the medical officer may not always see it in this light, is that failures almost inevitably return, if not to his own care, to some Service hospital, to be recorded on the man's medical documents.

It is with these advantages in view that an attempt has been made to analyse the cases of coliform bacillus urinary tract infection which occurred among Royal Air Force personnel from the beginning of the year 1926 till the end of 1936.

Source of cases under review.—The cases reviewed comprise, so far as possible, all instances of uncomplicated coliform bacillus infection of the urinary tract occurring during these eleven years. While these infections are not so common in males as they are in females, they are sufficiently common to form a serious source of wastage of man-hours. Notes of all cases likely to fall into the group have been extracted from the medical history envelopes in which all admissions to hospital or periods of sickness of over forty-eight hours' duration are recorded. A number of these patients have been under my own care. Some cases have certainly been missed, owing to the fact that either no culture of the urine was made or the record of the result was omitted. It is not thought, however, that such cases can be numerous.

Limitation of the cases to those showing a pure coliform bacillus infection has led to some artificiality. On occasion these bacteria may be secondary invaders only,

having overgrown the original infecting micro-organism, or an originally pure coliform bacillus infection may become superinfected by other micro-organisms. Again, in cases thought to be pure infections, the coliform bacillus has disappeared during treatment, some other micro-organism, usually *Streptococcus fæcalis*, appearing in the cultures. Hence it is by no means always easy to say that a given patient has a pure coliform bacillus infection. The majority of the urine cultures have been made from mid-stream specimens and the appearance of a few staphylococci in the culture, if absent from subsequent cultures, has been regarded as a contamination. In the Annual Report of the Health of the Royal Air Force the majority of these cases are classified under the heading of pyelitis or cystitis. These diagnoses include a number of cases with urinary symptoms from which those under review have been selected. Table I, which has been compiled from the Annual Reports, shows the number of cases classified under these two headings and the incidence per 1,000 of strength.

TABLE I.—CASES OF PYELITIS AND CYSTITIS IN THE ROYAL AIR FORCE IN THE UNITED KINGDOM, ABROAD, AND IN THE TOTAL FORCE DURING THE YEARS 1926 TO 1936.

	United Kingdom			Abroad			Total Force		
Year	Average strength	No. of cases	Incidence of cases per 1,000 of strength	Average strength	No. of cases	Incidence of cases per 1,000 of strength	Average strength	No. of cases	Incidence of cases per 1,000 of strength
1926	23,958	8	0·3	9,027	13	1·4	32,985	21	0·6
1927	21,526	12	0·6	8,597	15	1·7	30,123	27	0·9
1928	22,359	22	1·0	8,111	25	3·1	30,470	47	1·5
1929	22,685	8	0·4	8,474	11	1·3	31,159	19	0·6
1930	23,191	15	0·6	8,809	7	0·8	32,000	22	0·7
1931	23,492	22	0·9	8,956	14	1·6	32,448	36	1·1
1932	23,053	20	0·9	8,824	17	1·9	31,877	37	1·2
1933	21,874	13	0·6	8,994	15	1·7	30,868	28	0·9
1934	21,424	26	1·2	9,200	21	2·3	30,624	47	1·5
1935	25,242	20	0·8	9,856	18	1·8	35,098	38	1·1
1936	35,823	31	0·9	12,011	15	1·3	47,834	46	1·0
Yearly average	24,057	17·9	0·7	9,169	15·5	1·7	33,226	33·4	1·0

For comparison, Table II shows the cases of coliform bacillus urinary infection forming the series under review. It will be seen that these cases form roughly one-third of those diagnosed as cystitis or pyelitis.

TABLE II.—CASES OF COLIFORM BACILLUS URINARY TRACT INFECTION OCCURRING IN THE UNITED KINGDOM, ABROAD, AND IN THE TOTAL FORCE DURING THE YEARS 1926 TO 1936.

	United Kingdom			Abroad			Total Force		
Year	Average strength	No. of cases	Incidence of cases per 1,000 of strength	Average strength	No. of cases	Incidence of cases per 1,000 of strength	Average strength	No. of cases	Incidence of cases per 1,000 of strength
1926	23,859	2	0·1	9,027	3	0·3	32,985	5	0·2
1927	21,526	2	0·1	8,597	5	0·6	30,123	7	0·2
1928	22,359	4	0·2	8,111	4	0·5	30,470	8	0·3
1929	22,685	3	0·1	8,474	5	0·6	31,159	8	0·3
1930	23,191	5	0·2	8,809	2	0·2	32,000	7	0·2
1931	23,492	7	0·3	8,956	2	0·2	32,448	9	0·3
1932	23,053	6	0·3	8,824	2	0·2	31,877	8	0·3
1933	21,874	10	0·5	8,994	7	0·8	30,868	17	0·6
1934	21,242	12	0·6	9,200	6	0·6	30,624	18	0·6
1935	25,242	10	0·4	9,856	3	0·3	35,098	13	0·4
1936	35,823	9	0·3	12,011	3	0·3	47,834	12	0·3
Yearly average	24,057	6·4	0·3	9,169	3·8	0·4	33,226	10·2	0·3

Pathology.—Little is known about the morbid anatomy of the condition, because the vast majority of acute uncomplicated cases recover. It has been stated (Winsbury-White, 1933) that there is no evidence that pyelitis exists as a separate entity apart

from infection of the renal substance. Animal experiment, in addition to the well-known drawbacks in comparing the findings to human pathology, has been handicapped by the difficulty experienced in infecting the normal urinary tract. Recently Helmholz (1934) has found that the condition of simple pyelitis without renal involvement occurs spontaneously in rabbits. He has been able to study the condition in these animals and has shown that not only does simple pyelitis occur, but in uncomplicated cases there appears to be a barrier preventing infection of the kidney substance.

The infecting organism.—There is a tendency in British textbooks to class all Gram-negative bacillary urinary infections together as *Bacillus coli* infections. With the recent advances in treatment it has become apparent that a detailed knowledge of the type of the infecting organism is of more than casual interest. An infection resistant to treatment may be due not necessarily to some local complication but possibly to the fact that the bacteria causing the infection belong to one of the more uncommon types. Hill, Seidman, Stadnichenko, and Ellis (1929) studied 200 cultures of Gram-negative bacilli isolated from cases of genito-urinary infection. They divided them into four groups: (1) 100 organisms fermenting lactose with acid and gas production, a negative Voges-Proskauer reaction but positive methyl-red reaction, i.e. Escherichia cultures. (2) 79 organisms giving acid and gas in lactose media, a positive Voges-Proskauer reaction, but negative methyl-red reaction, i.e. aerobactor cultures. (3) Five proteus cultures. (4) 16 miscellaneous types. They noted that aerobactor strains are uncommon in ordinary fæcal cultures and suggest that they may be more virulent in their attack on the genito-urinary tract.

The cases from which these organisms were isolated were of a severe character, and it would unquestionably be of interest if bacteria from the type of infection seen commonly in Service hospitals were submitted to more detailed investigation.

Modes of infection and invasion.—One of the most interesting problems in the pathology of the disease is the mode of infection and the method of spread to the kidney. How these occur is still a subject of controversy. The hypothesis that there is a direct spread from the overlying gut seems now to be discredited, save in exceptional circumstances, and infection is believed to occur either through the blood-stream or by way of the lower urinary tract.

(1) *Hæmatogenous infection.*—From the analogy with the enteric group of fevers, it would seem that the blood-stream is a likely route of infection. It has been stated that a typical attack commences with generalized symptoms—such as malaise, alimentary disturbance, or, in some cases, a rigor—before the more localized symptoms occur. Rigor, in particular, has been adduced as evidence of blood-stream invasion (Morson, 1937). There was a rigor at onset in seven patients in this series of 112 cases. At the onset of the majority of acute cases, symptoms of general malaise occurred coincidently with localized symptoms. In 34, some one symptom preceded the others; in 22 it was frequency or pain on micturition, in 10 it was lumbar pain, and in two hypogastric pain. It has, however, been stated that frequency and pain on micturition are not necessarily evidence of lower urinary tract infection, since these symptoms may occur in primary renal involvement.

From the laboratory aspect, the evidence largely depends on the finding of positive blood cultures at some period during the disease. Panton and Tidy (1912) isolated the *Bacillus coli* in three cases of bacilluria, one of which was apparently uncomplicated. Scott (1929) reported 82 cases of positive blood-stream infection in urological patients, but 51 of these were after operation and 28 after some form of instrumentation. Not one of the three remaining cases was an uncomplicated case of bacilluria. Hyman and Edelman (1932) similarly reported 64 positive blood cultures, but only two of uncomplicated pyelitis. Evidence of successful blood culture from the type of patient met with in the series under review appears to be lacking. There is also much experimental evidence to show that bacteria injected into the subcutaneous tissues, or

placed on the surface of mucous membranes, pass rapidly into the lymphatics and thence into the blood-stream. Kidd (1920) has brought forward evidence from the study of spontaneous and accidental infections in the human being and from other sources strongly supporting the theory of hæmatogenous infection. Against this it has been argued by Helmholz (1937*b*) that the presence of coliform bacilli in the blood does not necessarily mean that the urinary organs have been infected by this route, and that intravenous injection of bacteria, even after the kidney has been damaged, does not necessarily cause urinary infection.

(2) *Ascending infection.*—The greater liability of women as compared to men to suffer from the disease is often put forward as indirect evidence that the path of invasion is via the lower urinary tract (Table III). This increased liability has been explained as being due to the shorter length of the female urethra and the greater danger of contamination from the rectum. The explanation seems all the more likely when it is remembered that the striking difference of ratio in the two sexes is confined to bacillary and is not shown in coccal infections. The position is, however, complicated by the fact that certain conditions occurring only, or more often, in the female, such as pregnancy and the abuse of purgative drugs, are believed to predispose to the disease. While this is true in adults, these factors do not operate in children in whom the greater incidence in girls is almost as striking as it is in women. It is difficult to avoid the conclusion that anatomical differences play an important part in the ætiology of the disease.

TABLE III.—INCIDENCE OF COLIFORM BACILLUS URINARY INFECTIONS IN MALES AND FEMALES GIVEN BY DIFFERENT OBSERVERS.

Name of observer	Age-group	Number of cases	Number in males	Percentage in males	Number in females	Percentage in females
Band (1933)	Adult	136	29	21	107	79
Cross (1937)	Adult	470	121	26	349	74
Hellström (1924) ...	Adult	133	13	10	120	90
Ryle (1932)	Adult	53	13	25	40	75
Total ...		792	176	22	616	78
Beer and Hyman (1930)	Children	703	166	24	537	76
Campbell (1934) ...	Children	402	110	27	292	73
Hellström (1924) ...	Children	66	5	8	61	92
Schwartz (1918) ...	Children	38	6	16	32	84
Total ...		1,209	287	24	922	76

Helmholz (1937*b*) has done much experimental work on the subject and has recently summarized some of his conclusions. Despite the fact that infection of the normal bladder in man or in rabbits is difficult, he has been able to show that it is possible with specially virulent bacteria. Spread of infection to the kidney was also accomplished experimentally following bladder infection but the method of ascent was by no means certain, histological examination of the ureters having shown evidence of peri-ureteral inflammation in only three out of 13 animals. Cabot (1936) thought that the evidence pointed to spread in the submucosal or in the muscular or peri-ureteral connective tissues, although no direct evidence has been brought forward to support this view.

Many series of experiments have been done on animals, chiefly by injecting some coloured substance into the lower parts of the urinary tract and tracing the subsequent course of the particles of the dye. Winsbury-White (1933), after a series of experiments, concluded that "the main pathway was in the lymphatics of the outer coat of the ureter and in the peri-ureteral zone". On the other hand Mackenzie and Wallace (1935), after a somewhat similar series, state that "in every case the dye passed to the lymphatic chains running up along the aorta. No dye could be found in any instance passing up the ureteral wall or along the peri-ureteral lymphatics".

One series of experiments by these authors suggested that the dye passed from the aortic glands upwards to the thoracic duct and thence via the blood-stream to the kidneys. In uncomplicated cases ascent of infection by way of the lumen of the ureter is suggested by Learmonth (1937) as the most attractive hypothesis, and is the conclusion to which Helmholz has come as the result of his many experiments. From the evidence available it seems probable that both the hæmatogenous and the ascending route of invasion can occur, but the pendulum appears to be returning to the original conception that in most cases infection starts in, and ascends from, the lower urinary tract. Clinical evidence in support of either hypothesis is difficult to produce, but in studying the medical history of these cases certain suggestive points have arisen.

Coital infection.—Cases of coliform bacillus urinary infection occurring among young recently married women, quite apart from pregnancy, have often been described. A complicating factor of infection under similar circumstances in males is the possibility that coitus has awakened a latent vesicular, prostatic, or urethral infection. In this series eight patients gave a history which suggested some direct relation between the coliform bacillus infection and coitus. Two cases occurred within a few days of marriage. In one of these cases the wife was examined and her urine found to be sterile on culture. In two further instances the wife was found to have a *Bacillus coli* urinary infection.

Non-specific urethritis.—One rather striking factor has been the occurrence in some patients of a urethral discharge, slight in amount, and transient in character, often immediately preceding the onset of more general symptoms. These patients have inevitably been taxed with the possibility of coital infection and some have, at first, been admitted to the venereal wards. A majority have strenuously denied exposing themselves to infection and in certain cases seen personally I felt convinced that they had not recently, or had never, exposed themselves. Thirteen patients were found to have a urethral discharge of this type, usually mucoid but sometimes semipurulent. Unfortunately, the laboratory reports on the urethral smears in these patients usually noted the absence of gonococci and the presence of secondary organisms without further note of their morphology. In one instance it was reported that the predominant organism in the urethral smear was a Gram-negative bacillus. Three of these patients were married and had had recent connexion with their wives. They had been in the Royal Air Force for seven and a half years, twelve and a quarter years, and twelve and a half years, respectively. In no instance was there a history of venereal disease or of any disease suggesting urinary tract infection. The remaining 10 patients were unmarried. One had a history of epididymitis eleven years previously for which no cause had been found. In nine there was no history of venereal disease or of any condition suggesting urinary tract infection. The medical history of these 10 patients was available for an average period of seven and a half years, the shortest period being three years, the longest thirteen years. It seems possible that this slight discharge occurred in a greater number of patients but, owing to its small amount and transitory character, was overlooked.

These clinical points are open to more than one interpretation and they afford no evidence as to the mode of spread, but they suggest that the lower urethra is the portal through which the original infection enters.

Ætiology.—Of the 112 cases, 28 occurred among officers and 84 among airmen. The incidence of the disease among the airmen by age-groups is shown in Table IV. From this table it will be seen that the incidence increased in the higher age-groups. There does not appear to be any reason why officers should be more prone to the disease than airmen, and the higher rate for officers would appear to be attributable to the fact that during the period under review there was a much higher percentage of officers in the over-30 age-group (roughly 50% of all officers over 20 years of age) than there were airmen (roughly 20% of all airmen over 20 years of age).

TABLE IV.—INCIDENCE BY AGE-GROUPS OF 84 CASES OF COLIFORM BACILLUS URINARY TRACT INFECTION AMONG AIRMEN, OCCURRING IN THE UNITED KINGDOM, ABROAD, AND IN THE TOTAL FORCE DURING THE YEARS 1926 TO 1936.

Age last birthday	Home: Man-years exposed to risk	Home: Cases	Abroad: Man-years exposed to risk	Abroad: Cases	All areas: Man-years exposed to risk	All areas: Cases	Cases per 1,000 man-years: Home	Home (combined)	Abroad	Abroad (combined)	All areas	All areas (combined)	Age last birthday
Airmen													*Airmen*
Under 18 ..	20,000	1	—	—	20,000	1	0·1		—		0·1	0·12	Under 18
18 - 19 ...	36,300	6	700	—	37,000	6	0·2		—		0·2		18 - 19
20 - 21 ...	38,500	8	10,800	1	49,300	9	0·2		0·1		0·2		20 - 21
22 - 23 ...	30,900	9	23,000	8	53,900	17	0·3	0·2	0·3	0·3	0·3	0·25	22 - 23
24 - 25 ...	29,500	5	21,700	7	51,200	12	0·2		0·3		0·2		24 - 25
26 - 27 ...	24,400	5	10,800	4	35,200	9	0·2	0·2	0·4	0·3	0·3	0·24	26 - 27
28 - 29 ...	17,200	4	5,700	1	22,900	5	0·2		0·2		0·2		28 - 29
30 - 34 ...	23,100	10	9,900	2	33,000	12	0·4	0·4	0·2	0·4	0·4	0·36	30 - 34
35 - 39 ...	10,700	3	4,900	4	15,600	7	0·3		0·8		0·4	0·45	35 - 39
40 and over	6,300	3	2,300	3	8,600	6	0·5		1·3		0·7	0·70	40 and over
All ages ...	236,900	54	89,800	30	326,700	84	0·2		0·3		0·3	0·26	All ages
Officers													*Officers*
All ages ...	27,700	16	11,100	12	38,800	28	0·6		1·1		0·7	0·72	All ages
All ranks													*All ranks*
All ages ...	264,600	70	100,900	42	365,500	112	0·3		0·4		0·3	0·31	All ages

In view of the uncertainty of the mode of invasion and the path of spread, it is difficult in any given case to find a cause for the attack, although Dunlop (1937), in a study of the history of 68 cases of urinary infection, states that "even in the absence of an obstructive lesion, an infective focus or some other definite ætiological factor can usually be found". It is possible in most cases, by close questioning, to obtain a history of some alimentary disturbance, especially overseas, but it is by no means certain that there is a connexion between this and the urinary infection. Of the conditions usually considered to have a direct ætiological relationship with coliform bacillus infections of the urinary tract, diarrhœa is one of the most common. Schwartz (1918) examined 63 infants with various gastro-intestinal diseases, and found that 38, or 60%, showed the presence of Gram-negative bacilli in the urine. Nearly everyone suffers to a greater or less extent from diarrhœa during their tour of service abroad. The incidence of enteritis among the Royal Air Force personnel overseas, quite apart from the many mild cases never reported, is approximately ten times greater than among the personnel at home. It might, therefore, be imagined that the incidence of coliform bacillus infections of the urinary tract among the personnel abroad would be considerably higher than at home. From Table II it has been seen that while the incidence abroad was slightly higher than at home, the difference was not significant. When corrections have been made and the rates for the various age-groups at home and abroad compared (Table IV), there has been even less difference. From these figures service overseas does not appear to have any influence on the incidence of the disease.

In one case in the series a cause could be more or less definitely assigned, infection having followed catheterization. A history of gonorrhœa, which might have served as a basis of infection, was not common. There were four patients with a history of gonorrhœa, in one instance sixteen years, in two nine years, and in one eighteen months before the onset of the coliform bacillus infection. It is to be noted that besides the history given by the patient, medical records were available for all cases for a period which averaged seven and a half years with a maximum of twenty-two years ten months, and a minimum of twelve days. In addition, two cases had chronic prostatitis. From one of these two cases—an extremely persistent coliform bacillus

infection—a specimen of prostatic secretion was found to contain a schistosome egg. Following a course of antimony tartrate injections, the infection eventually cleared up. In five instances a chill was thought to have been the predisposing factor, while in three the history suggested that an attack had occurred some years previously.

Few of my own patients showed any obvious evidence of lowered resistance and some were of good physique, with healthy complexions, and gave no history of irregular bowel action.

Symptoms.—As regards the clinical course of the disease these patients could be divided in two groups.

Group I, comprising 95 cases, showed an acute onset with urgent urinary symptoms, usually responding well to treatment. In *Group II*, comprising 15 cases, the onset was not so acute, the symptoms were less marked, and treatment was more difficult. In some of these cases there had almost certainly been a previous acute attack which was not reported or had not been diagnosed.

Two cases were treated at home for some period by civil medical practitioners, and symptoms had disappeared before admission to hospital, although bacilluria was still present. No notes of the original symptoms are available and these two cases have been omitted.

The frequency of the symptoms is shown in Table V. Although the numbers

TABLE V.—FREQUENCY OF SYMPTOMS NOTED IN 110 PATIENTS WITH BACILLURIA.

Symptom	Group I	Percentage	Group II	Percentage
Pyuria	95	100	15	100
Hæmaturia	45	47	4	26
Frequency of micturition ...	72	76	3	20
Pain on micturition	75	79	4	26
Pyrexia	67	70	5	33
Pain—back	59	62	8	33
,, —rt. loin	13	14	4	26
,, —lt. loin	14	15	1	7
,, —hypogastrium	22	23	2	13

in the two groups are in no way comparable owing to the small number in group II, the table shows that the relative frequencies of the symptoms in this group are generally less than in group I. In every case in group I there was either frequency of micturition or pain during or after micturition. In the majority both of these symptoms were present. The incidence of pyrexia should be higher than is shown in the table owing to the fact that some patients were treated for the first few days in their own homes and no record of the temperature for this period is available. On admission to hospital the temperatures were found to be normal. It is usually stated that the pain in the right loin is more common than in the left, but in the cases with acute onset both sides were affected in almost equal proportion.

Prognosis.—The prognosis in the majority of cases is undoubtedly good, and many patients will recover spontaneously. Infection may, however, lie dormant for many years after apparently successful cure, and a fact that cannot be over-emphasized is that one or more sterile urine cultures is no criterion of cure. The need of caution in prognosis has been pointed out by Wharton Gray and Guild (1937) who studied the late effects of pyelitis in a number of girls who had had the disease on an average thirteen years previously. Of the 30 cases only 13 were completely normal. The remaining 17 had either some urinary abnormality or symptoms referable to the urinary organs.

The final result in the cases under discussion among Royal Air Force personnel, so far as it is known, is shown in Table VI. In this group of 97 cases with acute onset 18 had one or more relapses after treatment, in hospital. Five of these cases passed

from observation, being either discharged or invalided from the Service with coliform bacilli still present in the urine. Four cases still serving are known not to be cured. The 88 patients thought to have been cured have been under observation since discharge from hospital for an average period of nearly four years, with a maximum of eleven and a quarter years and a minimum of one month. Of 15 patients with symptoms of gradual onset, seven had one or more relapses after treatment. One airman passed from observation with coliform bacilli still present in the urine, and one is still serving and is known not to be cured. The 13 cases in this group, thought to be cured, have since been under observation without relapse for an average period of just over four years with a maximum of nine and a half years and a minimum of one year.

TABLE VI.—NUMBER OF PATIENTS THOUGHT TO HAVE BEEN CURED.

Type	Number	Thought cured after first admission to hosp.	Per-centage	Number relapsing	Per-centage	Relapses thought cured after further treatment	Total thought to have been cured	Per-centage	Average period of subsequent observation in months
Acute onset	97	79	81	18	19	9	88	91	46·2
Gradual onset	15	8	53	7	47	5	13	86	50·0
Total	112	87	78	22	22	14	101	90	46·7

While it is difficult to say that any given patient has been cured, in 101 of the 112 cases, there is no record of relapse in a period of observation following the attack which averaged 3·9 years.

Treatment.—Owing to the fact that the cases under review occurred during a period extending over eleven years, the treatment rather naturally falls under three heads: (1) That previous to the introduction of the ketogenic diet. (2) The ketogenic diet. (3) Mandelic acid treatment. To these must be added a fourth, treatment by sulphanilamide, which has, however, been introduced too recently for use in any but a few of these patients.

All patients require a thorough clinical and urinary investigation, with a search for any localized focus of infection such as may result from coincident bowel upset, which will need the appropriate treatment. In practice it is usual, after these investigations, to try the effect of treatment before submitting the patient to a complete urological investigation, unless some definite contra-indication is present. If resistant to treatment or showing a tendency to relapse, a complete urological overhaul is necessary. All patients should, moreover, be re-examined after a lapse of some weeks, and further urine cultures done whether symptoms have recurred or not.

(1) Treatment previous to the introduction of the ketogenic diet. The simplest of the many forms of treatment which have at one time or another been recommended is probably that of flushing the urinary tract by making the patient drink large amounts of water. Numerous patients have apparently benefited by this method of treatment, though the direct therapeutic effect must be slight and any instance of cure largely spontaneous in nature. The commonest form of treatment has been by means of alkalis, and effective alkalinization of the urine is usually followed by a rapid decline in the severity of the symptoms, though, at first, with but little diminution in the number of bacilli in the urine. Of the other means of treatment falling into this group, hexamine with acid sodium phosphate and vaccines have been largely used. Many patients have been relieved of their symptoms and eventually cured when treated by these methods, but how far this has been due to the treatment it is difficult to say.

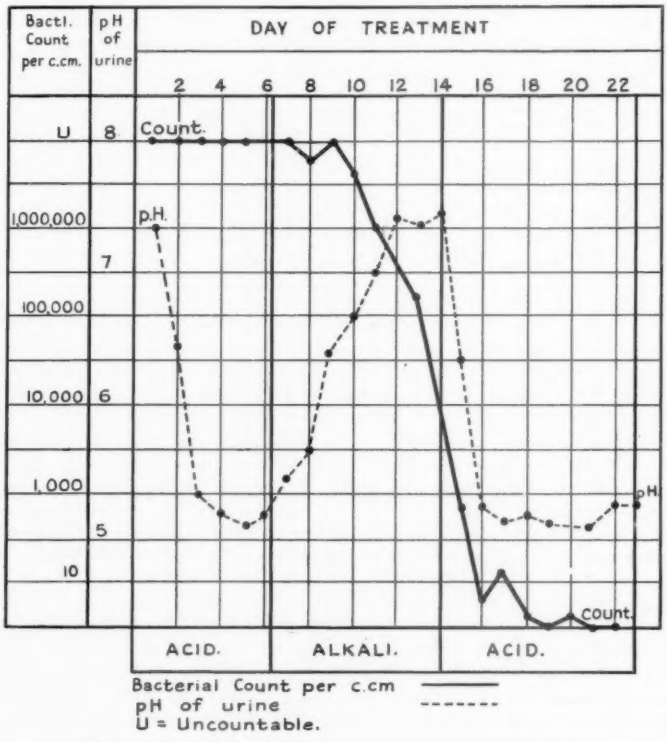
(2) The ketogenic diet as a method of treatment of urinary infections was introduced in 1931 (Clark, 1931; Helmholz, 1931), although a somewhat similar form of diet had been previously advocated. While there could be no doubt as to the efficacy of this treatment, it suffered from the disadvantage that the diet was nauseating in the extreme. It was owing to the difficulties experienced in this respect that another form of acidifying treatment was tried at the Royal Air Force Hospital, Halton, in 1932. A method based on the alternate use of alkalis and acid with hexamine mixtures has been advocated by many observers. By substituting ammonium chloride for the hexamine and acid, it was found that sterilization of the urine of some patients could be rapidly obtained. After the patient had been rendered afebrile, by means of alkalis, an ammonium chloride mixture was given for five or seven days, the alkali-acid cycle being repeated as often as necessary. Ammonium chloride and similar acidifying drugs given over long periods can be as unpleasant as the ketogenic diet, and it has been shown (Oppenheimer, 1935) that they may be dangerous to some patients. Given for short periods in suitable cases they do not appear to cause harm in therapeutic doses. It has repeatedly been pointed out that the acidity of the urine obtainable by means of drugs is incapable alone of causing a bacteriostatic or bactericidal effect. This was well brought out in one patient treated by this method in 1933. It will be seen from the accompanying chart that at the outset, despite a low pH of the urine, due to the ammonium-chloride treatment, there was no effect on the bacterial count. On the return to an alkaline mixture the count began to decrease, the fall being accentuated on the return once again to the acidifying drug.

(3) Mandelic acid therapy. Rosenheim in 1935 published the results of his research for some drug which when taken by the mouth would have a bactericidal effect similar to the ketogenic diet. He showed that such a result could be obtained by the action of mandelic acid in an acid urine. This form of therapy, in one or other of its modifications, has been used extensively and successfully, but has the drawback that in some patients it causes nausea or other toxic symptoms. It has been stated that it is almost always successful in non-obstructive cases of coliform bacillus infection. It was originally claimed that the urine was rendered sterile in ten to twenty days, but recently Helmholz and Osterberg (1937) have produced sterility in much shorter periods.

(4) Sulphanilamide therapy. Soon after the introduction of sulphanilamide it was reported by various observers (Butchel, 1937; Butchel and Cook, 1937; Helmholz, 1937*a*; Kenny, Johnston, and von Haebler, 1937) to be of value in the treatment of urinary tract infections, these results being subsequently fully confirmed. It has, moreover, the advantage of acting in an alkaline urine and can be used at the onset of the disease. Any form of treatment which acts only in an acid urine is best omitted during the febrile period. This drug can be given at an early period and, as it usually acts more rapidly, should cause a considerable saving in the period of a patient's ineffectiveness. It is also bactericidal to most of the organisms commonly infecting the urinary tract except *Streptococcus fæcalis*, which is fortunately attacked by mandelic acid. Sulphanilamide is, however, more toxic than mandelic acid, and a number of patients appear unable to tolerate it in therapeutic doses.

The present series of cases is too small, and the lapse of time since some of the patients have returned to duty is too short, to admit of any but the most tentative conclusions regarding treatment. In any event the period elapsing before a urine is rendered sterile, or the time for which a patient is in bed or in hospital, is an admittedly fallacious basis of comparison. Of the 97 cases with acute onset, 60 were admitted within a few days of the commencement of the disease and were kept in hospital until apparently cured. Not one of these patients has subsequently relapsed. The periods in hospital ranged from 16 to 168 days, with an average of 48·3 days.

In the small series of patients treated by the alternating acid-alkali treatment, the bacterial colony count in 1 c.c. of urine was reduced from several millions to zero in an average period of just under three weeks. In the few patients treated by the new methods in which comparison with the above cases appeared to be justified, the impression was gained that mandelic acid therapy shortened the average period by a few days, while sulphanilamide produced a sterile urine in an even shorter period. Two cases, which resisted various courses of treatment by the other methods, were cured by sulphanilamide in a few days.



To show the effect of acid-alkali therapy on the bacterial count.

Summary.—(1) One hundred and twelve cases of pure coliform bacillus infection of the urinary tract occurred during the period of eleven years in a male population of known size. (2) The morbidity rate over the whole period was 0·3 per 1,000 of population per annum, the incidence of the disease increasing in the higher age-groups. Service overseas, with the increased liability to intestinal upset, caused no significant increase in the incidence of the disease. (3) A majority of the patients were treated by the older methods—alkalis, hexamine, or vaccine. Nearly 90% were relieved of their symptoms in a comparatively short time and have remained free from

relapse during a period of observation of several years. (4) The newer forms of treatment, the ketogenic diet, mandelic acid, or sulphanilamide therapy, more rapidly produce a sterile urine. It is yet to be seen whether patients treated by these methods will show an increased or decreased freedom from relapse.

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Discussion.—The President said that infection with *Bacillus coli* might be superadded to some pre-existing disease. He cited a case of proved typhoid fever in which, at autopsy, cultures of *Bacillus coli* were obtained from the spleen and heart's blood, while *Bacillus typhosus* was recovered only with great difficulty and might easily have been missed. A wrong diagnosis might have been reached in this case. It was important to ensure that there was no other underlying condition in anomalous cases of *Bacillus coli* infection.

Wing-Commander T. C. Morton: At Group-Captain Rook's suggestion I carried out a short series of experiments on five healthy volunteers. A midstream preparation of urine was obtained after each twenty-four hours' treatment and the pH was estimated. 5 c.c. of the urine was cultured for twenty-four hours with a constant suspension of *Bacillus coli* from a strain isolated from a chronic case of *Bacillus coli* cystitis. The number of organisms before and after incubation was estimated and the difference recorded.

1st Series.—The following alkaline mixture:—

℞ Pot. cit.
Pot. bicarb.
Sod. cit.
Sod. bicarb. } aa gr. xx.

Aqua menth. pip.; ad 1 fl. oz.

was given t.d.s. for three days. In every case there was a marked increase in the number of

organisms after incubation for twenty-four hours, the average for 15 observations being a 3,212-fold increase in the number of organisms.

2nd Series.—Mandelix, 2 drm. in water was given four times a day before food; in addition a cachet of 15 gr. ammonium chloride was taken with the morning and evening dose. This was carried out for three days, and in every case there was a marked diminution in the number of organisms after incubation, the average for 15 observations being a 945-fold diminution in the number of organisms after incubation.

3rd Series.—7½ gr. of prontosil album were given t.d.s. for six days and in every case there was a marked diminution in the number of organisms after incubation, the average for 28 observations being a 909-fold diminution in the number of organisms after incubation. This is slightly inferior to the results obtained after mandelix but it was not considered justifiable to give these volunteers larger doses of prontosil album, although it was fully realized that the dosage given was considerably less than the optimum therapeutic dose.

Section of Urology

President—HENRY WADE, C.M.G., F.R.C.S.

[*February* 24, 1938]

Calcification of the Genito-urinary Organs

By JOHN SANDREY, F.R.C.S.

THE phenomenon of pathological calcification, namely the deposition of calcium salts in tissues other than bone, may be observed in most organs of the body under certain conditions. There is a tendency for any necrosed or diseased tissue, especially when it has undergone hyaline change, to become the seat of calcification. Cameron (1926) states that this is purely a mechanical process, determined by the abnormal physical conditions obtaining.

Of the genito-urinary organs, the renal parenchyma is the tissue most likely to be involved, as massive necrosis is a relatively common pathological change. It is most frequently observed in caseating tuberculous lesions and in degenerating neoplasms. In addition to this there is another mechanism, peculiar to the urinary tract, whereby calcium, the principal mineral constituent of the urine, is brought out of solution and deposited on the mucosa. The conditions necessary for this are present when the epithelium lining the urinary passages is altered or destroyed by disease, and clinically we find these changes taking place most frequently in the urinary bladder. The mechanism, again, is purely a physical one, and has been explained by Swift Joly (1929) according to the laws of surface tension. There is no surface tension between normal urine and normal transitional epithelium, and therefore no tendency for urinary salts to be deposited. Chronic ulceration of any kind, particularly when it is of long standing, may be followed, in the bladder, by the condition known as encrusted cystitis. Similar changes have been observed in the ureter and renal pelvis, but these are much less common sites. The encrustations are found only on the actual areas of ulceration and do not adhere to intact mucosa, where there is no surface tension.

Infection of the urine with urea-splitting bacteria, such as the *Bacillus proteus* or certain strains of staphylococci, may be the primary cause of the ulceration; more often it is a superadded factor. The urea-molecule is split to form ammonia and

carbon dioxide, resulting in the precipitation of calcium and magnesium phosphate in an alkaline medium. Thus chemical changes may influence the process to some extent, but that they are by no means essential to its occurrence is proved by the fact that many patients suffering from encrusted cystitis are found to be passing acid urine. These two processes are the means whereby calcium salts are deposited in the genito-urinary tract; the first comes under the heading of true calcification in the parenchyma, the second, for want of a better term, is referred to as "encrustation". They are quite distinct but may sometimes be observed taking place simultaneously in the same organ.

Calcification in the kidney (Plates I and II).—Calcification in the kidney is far more common in tuberculosis than in any other lesion and, so far as I am aware, it has never been observed in any other type of renal infection. Crenshaw (1930), in 1,817 cases of renal tuberculosis at the Mayo Clinic, discovered X-ray evidence of calcification in 131, or 7·1%. Braasch and Olson (1919) found positive shadows in 22% of 131 patients. In a series of 135 cases personally observed 44, or approximately one-third, were calcified.

As many of the shadows are small and barely opaque to X-rays, the quality of the plates and the preparation of the patient are of the greatest importance in demonstrating them.

Statistical evidence has shown that the older the patient, the greater is the tendency for tuberculous lesions to calcify and, of the two sexes, it is observed more often in men than in women.

Braasch and Olson (1919) make the following division :—

Group I.—Multiple small scattered areas seen as (*a*) irregular faint streaks; (*b*) punctate areas, often confined to one or other pole of the kidney (Fig. 1).

Group II.—Isolated areas exceeding 1 cm. in diameter which are often single but may be multiple (Fig. 2). They are generally indicative of caseating lesions which are localized to one part of the kidney. They vary in outline and in density, appearing as (*a*) shadows of irregular consistence and outline, likened to "filigree work"; (*b*) shadows uniform in density and even in contour, often very suggestive of stone.

Group III.—Large rounded or globular shadows outlining the whole or greater part of the kidney, resembling cumulus clouds in their appearance (Fig. 3). These shadows coincide with the presence of calcified deposits in dilated calyces which are filled with putty-like caseous débris. The opacities are often of variable density in different parts of the kidney. Some may be so soft and fluffy as to be hardly discernible. In other cases, they are more distinct and may form a complete cast of the kidney, a condition referred to as "total calcification".

The extent of the calcification is best appreciated by the study of stereoscopic films.

The process is an extremely slow one, as illustrated by a case at present under my care. In 1930, tubercle bacilli were found in the urine and intravenous pyelography showed an enlarged functionless right kidney. Conservative treatment in a sanatorium was carried out, owing to the presence of multiple tuberculous foci elsewhere. In 1935 a similar state of affairs was found with regard to the appearance and function of the kidneys. A few days ago an X-ray film showed faint rounded shadows of calcification beginning in the functionless kidney; the onset was therefore at least eight years after the organ was first affected by tuberculosis.

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PLATE I.

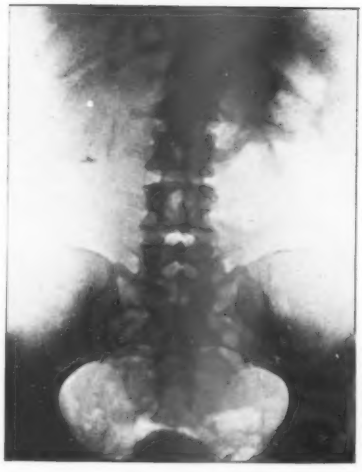


FIG. 1.—Calcification in renal tuberculosis. Braasch and Olson's classification—example of Group I.

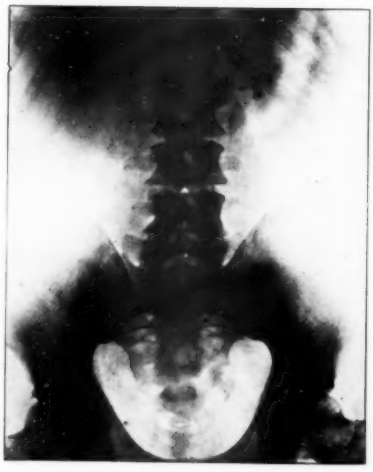
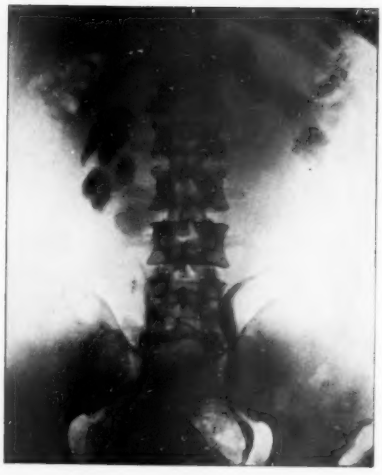


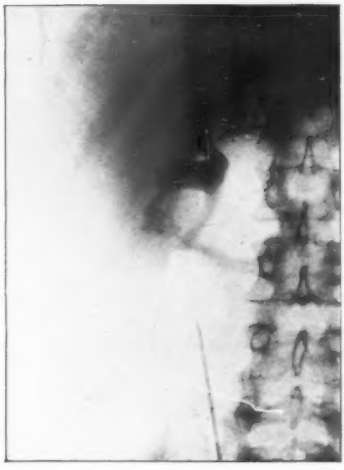
FIG. 2.—Example of Group II.

FIG. 3.—Example of Group III.

PLATE II.

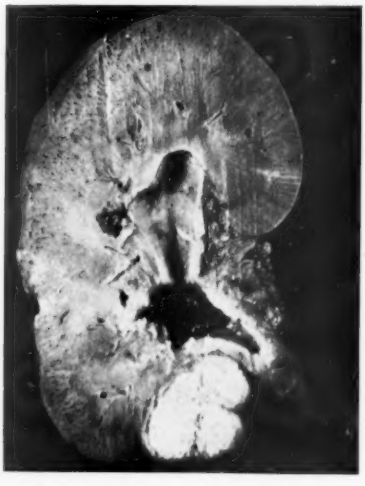


4*a*.



4*b*.

FIG. 4.—*a*, Loose phosphatic calculi in the left half of a horse-shoe kidney simulating calcification (antero-posterior radiogram and ascending pyelogram). *b*, Group of shadows in the lower pole of the right kidney, due either to parenchymal calculi or to tuberculous calcification. Painless right renal hæmaturia was the only symptom. No tubercle bacilli were found in the urine. No symptoms two and a half years after these pictures were taken.



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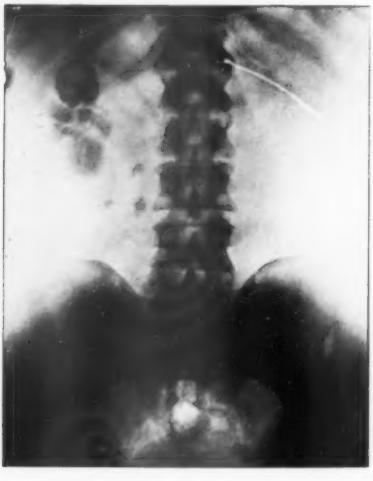

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FIG. 5.—Triangular calculus in pelvis of sectioned kidney adjacent to caseous area at the lower pole. The stone consisted of calcium phosphate.

FIG. 6.—Total calcification of the right kidney in a man aged 50 (under treatment three years for a gonorrhœal stricture). History of frequency and hæmaturia when aged 9 years; renal tuberculosis was diagnosed. Since then there has been no recurrence of symptoms. The general health is excellent. No tubercle bacilli were found in the urine. Cystoscopy revealed a retracted right ureteric orifice and no efflux of urine was seen.

JOHN SANDREY: Calcification of the Genito-urinary Organs.

The differentiation of these shadows, especially in Group II, may be difficult at times. Extrarenal opacities such as gall-stones, calcified hilar glands, enteroliths, calcified areas in the psoas or perinephritic region following chronic suppuration can in most cases readily be distinguished by means of lateral skiagrams or pyelograms. Confusion with stone will only occur in some shadows which are uniform in density and in outline and conform to the type described in Group II. Pyelography will identify these as being cortical in position whereas a calculus will be included in the pelvic outline.

Certain possible sources of error may be encountered : (*a*) Soft phosphatic calculi may resemble tuberculous shadows in outline (Fig. 4, *a* and *b*). (*b*) The rare parenchymal stone may lie far out in the cortex. (*c*) A true calculus may be present in a tuberculous kidney (Fig. 5). Calculi in association with renal tuberculosis are not uncommon. Eisendrath (1936) was able to collect 40 cases. In the present series calculi were present in four out of the 89 kidneys which were removed at operation.

The stones may be either primary or secondary. Primary calculi are generally large in comparison with the stage of the tuberculous focus found in the kidney. Their chemical composition varies as with other calculi. Evidence has been brought forward by Sermet (1930) to show that a renal calculus in a tuberculous patient is liable to be followed by a tuberculous infection of the pelvis in its vicinity. The dangers of performing pyelolithotomy in such cases are obvious. Moreover, it is clear that a careful bacteriological examination of the urine is essential in every case of calculus with pyuria, especially if the patient is known to have foci of tuberculous infection elsewhere.

On the other hand, secondary calculi are small in comparison with the extent of the tuberculous lesion. Many are merely calcified caseous masses which have become separated from the tuberculous process and do not attain the dignity of calculi. Larger true calculi may be found ; they are always phosphatic in composition.

It will be seen that calcification and secondary calculi are both the result of similar changes in caseous material, and this explains the fact that the two conditions are generally associated. Moreover, the shadows appearing in radiograms are of similar density and can rarely be distinguished from each other. The four cases in this series are all of the secondary variety and the largest is no bigger than a marble.

Although the part played by radiology in the investigation of renal tuberculosis is a subsidiary one, the study of an X-ray film is recommended as a routine procedure in every case and may yield valuable information, as the following instances show :

(1) When undoubted calcification is present in both kidneys and tubercle bacilli are found in the urine, further investigation is rendered unnecessary, for the condition is obviously bilateral.

(2) Renal calcification in cases of sterile pyuria must always suggest a diagnosis of renal tuberculosis.

(3) When evidence of total destruction of the kidney is present, nephrectomy is unlikely to benefit the patient. In such a case sections of the kidney show that all parenchyma have been replaced by caseous amorphous matter completely surrounded by a fibrous capsule ; the renal pelvis is represented by a mass of fibrous tissue and the upper end of the ureter is occluded.

The clinical term " autonephrectomy " has often been loosely applied to cases of closed renal tuberculosis, in spite of the fact that the infection is still active and that destruction of the parenchyma is by no means complete. The use of this term should be restricted to those cases in which there is complete absence of renal function together with total calcification (Fig. 6). The removal of such an organ is as unjustifiable as would be the removal of a calcified mesenteric gland.

The renal pelvis rarely becomes calcified but may, in advanced cases, become obliterated by fibrosis. Encrustations, secondary to chronic ulceration, may sometimes outline the pelvis and appear in X-rays as a " cast " of that structure.

Of the non-tuberculous conditions which may undergo calcification, hypernephroma is by far the commonest in this country. When calcification occurs the tumour is usually very extensive and the change is observed in the centre where necrosis has taken place (Plate III, Fig. 7). Hence, calcification of a hypernephroma is to be regarded, on the whole, as an unfavourable prognostic sign. Of the 25 cases of hypernephroma in this series, calcification was observed in three.

Calcification sometimes occurs in cysts of the kidney and the type most subject to this change is the hydatid cyst. Deposits form in the thickened adventitia in long-standing cases. According to Lee-Brown (1930) this is only an occasional phenomenon and cannot be expected in early cases.

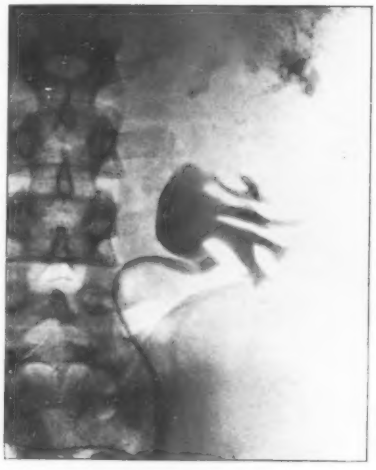
The ordinary solitary cyst does not tend to undergo calcification, but traumatic cysts may do so. Abbott (1892) reported an interesting case of this nature. The patient, who had suffered from hæmaturia fifteen years previously following a kick in the loin, was found to have an enlarged kidney in which egg-shell crackling could be felt on deep palpation. An old hæmatoma undergoing extensive calcification was removed at operation.

Calcification in the renal tubules has been produced experimentally by ligature of the renal artery in rabbits. Similar changes have been observed after poisoning by corrosive sublimate. Deposition of calcium salts in the tubules may occur in parathyroid disease and certain cases of renal dwarfism. Such changes are merely due to precipitation of calcium salts which are being excreted in concentrated form and, like uric acid " infarction " in the kidneys of infants, are transitory phenomenona.

Calcification in the ureter (Fig. 8).—Calcification in the ureter is rare but may occur in some cases of tuberculosis and bilharziasis. It is generally produced by the second mechanism, in which encrustations form on ulcerated areas in the ureteral mucosa. The ureter is nearly always dilated and it would appear that urinary stasis plays an important part in the process. Braasch and Olson (1919) state that calcification in urinary tuberculosis tends to involve a considerable portion of the ureter, the lower end being more frequently affected. The duct is often very thickened and may be palpable.

Calcification in the bladder (Fig. 9).—True calcification of the bladder-wall is rare outside those countries in which bilharziasis is endemic. In these cases aggregations of calcium salts tend to form around ova in the muscular layer and, in addition, there is surface deposition on the ulcerated mucosa. X-rays will often show two irregular concentric shadows, a centimetre or so apart, resulting from these two separate processes. True calcification of the bladder-wall may also occur in tuberculous cystitis ; more often, however, X-ray shadows in this region will be shown by cystoscopy to be due to encrustations within that viscus.

PLATE III.



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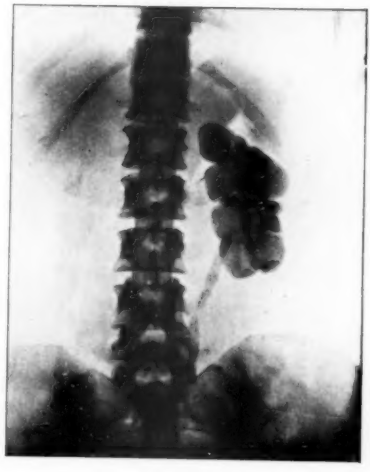

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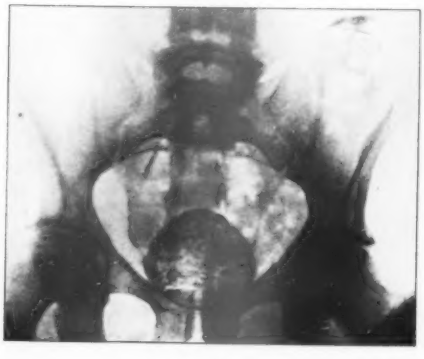
FIG. 7.—Calcified hypernephroma. The tumour was very large and extensively necrosed. It recurred soon after removal.

FIG. 8.—Tuberculous calcification of the left kidney and upper half of the left ureter. The first of a series of radiographs taken after injection of uroselectan B, in a middle-aged woman who complained of pain in the right loin. There had never been any disturbance of micturition or pain on the affected side. (Mr. Swift Joly's case.)



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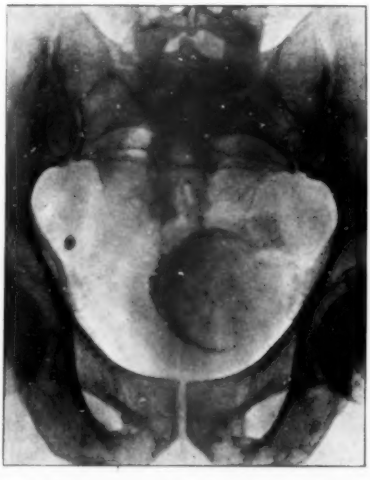

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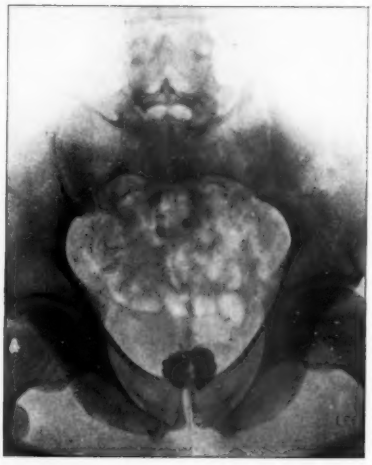
FIG. 9.—Calcification in bladder-wall with total calcification of left kidney (tuberculous). "Cystoscopy showed a smooth mucous membrane, looking as though it had been stretched for a long period. No tubercles or ulceration present. The contractile-power of the bladder-wall had gone. Capacity about 8 oz. No marked frequency, patient able to hold his urine from three to four hours. At the time of cystoscopy the urine contained no tubercle bacilli, though it had done so previously". (Case of Mr. Clifford Morson and Mr. W. H. Ogilvie.)

FIG. 10.—Encrusted carcinoma of bladder. The tumour was pedunculated, the pedicle being about the thickness of the index finger. The urine contained no pus and was sterile on culture. (Mr. F. J. Barrington's case.)

PLATE IV.



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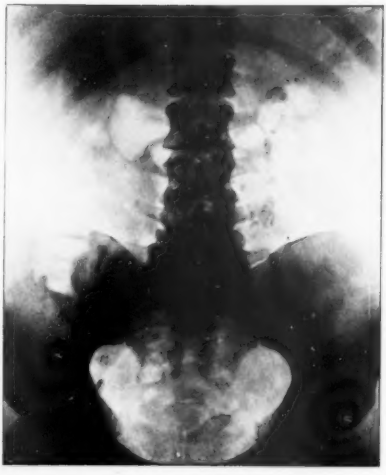

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FIG. 11.—Tuberculous calcification of the prostate in a man aged 36 who had had frequency and difficulty of micturition for fourteen years. It was associated with closed right renal tuberculosis. Marked clinical improvement following nephrectomy. Urinary difficulty was relieved by gentle dilatation of the rigid contracted posterior urethra.

FIG. 12.—Tuberculous calcification of the seminal vesicles. There were no special symptoms arising from the genital tract; the condition was associated with renal tuberculosis and was discovered during the course of routine investigation. The affected vesicles were easily palpable *per rectum*.

FIG. 13.—Senile calcification of the vasa deferentia. From a man aged 84, admitted in 1844 on account of traumatic cellulitis of the leg. At autopsy a bilateral hæmatocœle was found and the aorta was very atheromatous. (X-ray photograph of the specimen from the museum of Guy's Hospital.)

In encrusted cystitis the condition is confined to the mucosa. It may occur insidiously, but is more often a sequel to long-standing cystitis, ulceration of any kind, foreign bodies, neoplasms (Fig. 10), or leucoplakia. The term " alkaline encrusted cystitis " has sometimes been applied. This is not strictly in accordance with the findings, as urea-splitting bacteria do not appear to be essential for the precipitation of alkaline salts, in fact a large percentage of the urines are found to be acid. The varying degrees of surface tension between the altered mucosa and the urine are, as already mentioned, entirely responsible for the formation of encrustations, and it is not necessary to suppose that chemical changes must play an important part in the process.

Randall and Campbell (1937) describe two clinical types : (1) A localized flat area which appears as a greyish membrane and imparts a gritty sensation to an instrument. (2) Nodular elevated areas of crystalline débris, more pronounced on the bladder-base, either single or multiple, and firmly attached to the underlying ulcerated mucosa. The lesions are always discrete with intervening areas of intact but inflamed mucosa forming " bridges " between the encrustations.

It is essential to carry out a full renal investigation in every case of encrusted cystitis in order to eliminate renal infections, tuberculous or otherwise. In this series five cases of encrusted cystitis have been observed. Three were tuberculous in origin and another was due to persistent infection by a coliform bacillus. The fifth was the only case of the series in which the urine was found to be alkaline and a urea-splitting staphylococcus was grown on culture.

Calcification in the genital organs (Plate IV).—Compared with that of the urinary organs, involvement of the genital tract is relatively rare and is of little clinical importance. Again, calcification is nearly always the result of tuberculosis. When it occurs in the prostate gland the X-ray appearances may closely resemble those of prostatic calculi. The shadows, however, tend to be more uniform, they are soft in density and rounded in outline (Fig. 11).

The seminal vesicles are more often affected than the other genital organs and show stippled or granular shadows in radiograms (Fig. 12). Calcification of the wall of the vesicle must be differentiated from stone-formation in the lumen ; in the latter condition the opacities are always larger and more dense ; furthermore, it is usual to find evidence of involvement of other genito-urinary organs in cases of tuberculous vesiculitis. A calcified vesicle may sometimes cause errors in diagnosis as a localized indurated area felt *per rectum* may be mistaken for a hard neoplasm of the prostate or base of the bladder. Kretschmer (1922) reported a case of extensive calcification of one seminal vesicle in a boy aged 14, in which the mistaken diagnosis of vesical calculus was made. An unnecessary suprapubic cystotomy was performed, and the resulting fistula healed only after a closed tuberculous pyonephrosis had been removed.

The vas deferens is occasionally found to be involved in tuberculous calcification, and calcareous deposits may be found in the muscle-coat as a result of senile degenerative changes (Fig. 13). Chiari, who gave the first accurate description of this condition in 1903, observed three cases in elderly men during the course of routine post-mortem examinations. In all three the process involved the ampulla of the vas and in one the left vesicle was partly calcified.

The rarity of calcification in tuberculosis of the testicle is presumably due to the fact that caseating lesions tend to soften rapidly and discharge on the surface. Calcification is essentially a slow process and thus seldom occurs.

Areas of calcareous degeneration are sometimes found in the thickened walls of old-standing hydroceles.

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Section for the Study of Disease in Children

President—T. Twistington Higgins, O.B.E., F.R.C.S.

Meeting held at the Infants Hospital, Vincent Square, London, on February 25, 1938.

Some Clinical Observations on a Series of Cases of Acute Gastro-enteritis; with Special Reference to Treatment

By Mary J. Wilmers, M.D.

An interest in, at least, the more practical aspects of gastro-enteritis, such as the treatment and control of spread of this disorder, is forced on anyone working in a hospital for infants.

It was partly with a view to limiting spread of infection and partly in order to have an opportunity of studying the disorder from the therapeutic angle, that it was decided, in April 1937, that all cases of gastro-enteritis should be admitted under Dr. Maitland-Jones, and that any developing the condition while in hospital should be transferred to his care. For this purpose four single rooms were set aside. The nurses staffing these four rooms, with the exception of the sister of the ward—and, in her absence, the senior staff nurse—did not attend any other cases. Strict barrier nursing was employed and gowns, but not masks, were worn.

Since July 1937 any infant in the hospital showing symptoms suggestive of the onset of an attack of acute gastro-enteritis was transferred on suspicion to one of these four rooms. A certain number of these were sent back to their original ward after a few days' observation.

The 30 cases reported here occurred between May and December 1937. They were all in babies severely and acutely ill with gastro-enteritis, and treated with continuous intravenous saline infusion.

The observations on this rather short series are purely clinical. Twenty-five of these 30 babies were admitted with diarrhœa or vomiting or both. Five were admitted for other diseases as follows: Two infantile eczema; two feeding cases; one bronchitis; these were transferred to us at varying periods after the onset of symptoms of gastro-enteritis.

Ætiology

In considering the possible ætiology of the condition, the following points were especially noted in the history:—

(1) History of exposure to infection. Some sort of history was obtained in 16 cases. In three, the mother had a slight febrile illness just before the onset of symptoms in the infant; eight acquired the disease in this hospital; three came from other institutions for babies, and both these groups were considered to have been exposed to infection.

In two cases there was a definite history of contact with a baby suffering from gastro-enteritis at home.

(2) Number of children in family: It was thought that many of these babies would be found to come from homes in which there were several other children, in which case one might suppose that the general care and hygiene of the infant were at fault. In actual fact the majority of our cases were either only children, or there was one other child. The findings in this respect were thus entirely negative.

(3) Previous feeding: One very definite ætiological, or predisposing, factor was clearly shown in that not one of the 30 infants was entirely breast-fed at the time of onset of the disease. Two of them, twins, were partially breast-fed and complementary feeds of a cereal mixture were also given. An analysis of the artificial foods used did not implicate any one food. Various types of dried milks, sweetened and unsweetened condensed milk, and cow's milk mixtures had been employed.

(4) Age: All the infants, except one aged 1 year and 2 months, were under 1 year of age. 24 (66%) were under 6 months.

(5) Seasonal incidence: The 30 cases were spread out evenly over the six months May to December. No seasonal increase during the hot months could be made out.

(6) Parenteral infection: Before treatment was begun all cases were carefully examined for evidence of parenteral infection. This was found in nine cases (30%). Three had some evidence of otitis media which varied from a slightly infected drum to purulent aural discharge; three had a mild pharyngitis; two had bronchitis; one had early signs of pneumonia.

In the remaining 21 cases no evidence of parenteral infection was found. This figure (30%) for parenteral infections agrees with that found at post-mortem examination, if we exclude bronchopneumonia as being in most cases a late complication. 12 of the 30 cases came to autopsy. Of these, one had definite pus in both mastoids; one had a purulent bronchitis; one had an abscess of the face, with septic infarcts in the kidneys. Seven had changes in the lungs, varying from slight hypostatic congestion to actual necrosis of lung-tissue in one case; in this latter the lung condition was thought to be primary.

Treatment

Indications: In selecting these 30 cases for continuous intravenous therapy, considerable care was taken to choose only those infants thought to be very severely ill and unlikely to respond to the more usual forms of treatment. In a number the usual dietetic treatment, combined with hypodermoclysis, was tried for some days before we resorted to continuous intravenous therapy, and I think that if we erred it was on the side of withholding it too long.

The indication for continuous intravenous therapy was the presence of one or more of the following:—

Marked dehydration (21 cases); cyanosis (10 cases); clinical evidence of acidosis (6 cases). Of these symptoms cyanosis had the gravest prognosis, as in six of the 10 cases showing it the baby died. Three of the infants with clinical evidence of acidosis died, but the two who had the most outstanding hyperpnœa recovered.

Twenty-three cases showed some pyrexia; in seven the temperature at the onset of treatment was over 102° F.

Technique: The continuous intravenous solution was administered by means of the usual 300-c.c. graduated glass funnel, drip connexion, and rubber tubing, and a fine ureteric catheter inserted into the right internal saphenous vein. The right internal saphenous vein is the site of election for insertion of the catheter, but the left internal saphenous vein and the veins in the antecubital fossa were also used. A full-length catheter was used; it was inserted into the vein for two or three inches and tied in position with a catgut ligature. A small metal cannula connected the catheter to the rubber tubing and funnel.

The advantage in using a catheter rather than a needle or cannula is that the infant need not be in any way immobilized. Nursing is thus greatly facilitated and

the baby can be taken out of bed and nursed on the nurse's lap. This was done routinely every two to four hours in our cases ; I think it was an important factor in diminishing the incidence of hypostatic pneumonia.

The solution given was in all cases 5% glucose. In the first six cases this was given in Hartmann's solution, and in all subsequent cases in normal saline, which was changed after from twenty-four to forty-eight hours to half-normal saline. I could detect no clinical difference in results between the cases given Hartmann's solution and those given saline.

The quantity of fluid given was 2 oz. (60 c.c.) per lb. of body-weight in twenty-four hours. In those cases showing very marked dehydration 60–100 c.c. were given as quickly as possible at the beginning of treatment and not included in the total for twenty-four hours. In order to regulate the rate of flow the quantity to be given in one hour was calculated, and hourly readings of the fluid level in the flask were taken and noted.

Feeding : The infants were starved for a period varying from twelve to thirty-six hours, depending on the state of nutrition and age of the child. During this time the lips and mouth were moistened with water. When feeding was begun very small quantities—from 1-2 drms.—were offered two-hourly, alternating with an equal quantity of boiled water. The amount was increased by from 1-2 drms. every 12-24 hours, the water also being increased up to a total of ½ oz., after which no further increase in water was made. The feeds used were whole lactic acid milk mixture, preserved breast-milk, or Nestlés. The most satisfactory whole lactic acid milk mixture was made up as follows : Milk 1 pint ; sugar 1 oz. ; lactic acid 1 drachm. Breast-milk was used in a few very small babies, but I could not convince myself that the results were any better than with the above. Sweetened Nestlé's milk was made up in the proportion of 2 drms. to 1 oz. of water. It was assumed that it was the quantity rather than the quality of the feed offered which was important, and that it was therefore as well to give something of high caloric value. The amount of fluid given intravenously was decreased as that given orally was increased, so that the total fluid intake by the two routes remained constant at 2 oz. per lb. of body-weight. When the infant was taking the full quantity by mouth, the continuous intravenous drip was left running as slowly as possible (2–3 c.c. per hour) for twelve hours, before being discontinued.

Drugs : No drugs were used as a routine. In some cases kaolin was given, but I do not think that the infants were benefited by it. In two cases tincture of opium ♏i was given 4-hourly, and both cases showed definite symptoms of opium poisoning after 4 and 5 doses respectively.

Blood transfusion : In five cases a blood transfusion was given late in the course of the disease ; in three of these the infant died.

The immediate effects of the treatment were dramatic. Dehydration was diminished in all cases within 36 hours and often considerably earlier. The colour and pulse volume improved even more rapidly. Restlessness was relieved and the infant usually slept for the first 12 hours. The amount of urine passed was measured in all male infants. A free flow was established in 24-36 hours. In 24 cases the vomiting stopped immediately and in the remainder it was much diminished. The effect on the diarrhœa was less certain and more difficult to estimate.

Unfortunately the initial marked improvement was not always maintained. Relapses were fairly common when the babies were again taking a certain amount of food by mouth. In these cases a further period of starvation was enforced and feeding then started again from the beginning.

Some idea of the frequency of the relapses may be obtained by considering the average length of time these babies were given fluid intravenously, namely, nine days. The shortest period was three days and the longest twenty-two days, with

two intervals of thirty-six and fifty-two hours respectively. The longest continuous period was eighteen days. Both these latter cases ultimately made a good recovery.

The technical difficulties encountered in keeping the continuous intravenous solution running for so long were not very great. The commonest causes of trouble were blocking of the catheter, slipping of the ligature, with leakage of the fluid back into the bandages, swelling of the leg, which was disregarded so long as the intravenous solution continued to run, and thrombosis of the vein.

In 10 cases it was only necessary to use one vein ; in 15 cases two veins, and in five cases three veins, had to be used.

Complications

(1) Thrombosis of one or more veins. This occurred in 14 cases ; in one of these the thrombus went on to abscess formation but apart from this no untoward effects were observed.

(2) Anorexia was present to a greater or lesser extent in most cases. It occurred as soon as the larger quantities of food were given orally, and was at times so severe that the infant retched at the sight of food. Much skill in nursing, combined with the change from sweet to acid milk, or vice versa, was required to overcome it. In one or two cases it was necessary to give fluid by the intravenous route again.

(3) Bronchopneumonia occurred in 30% of our cases and was fatal in all.

(4) Hæmatemesis, which should probably be regarded as a symptom rather than a complication, was of the gravest prognostic import. Only one of our cases showing it recovered.

(5) Hæmorrhage *per rectum* occurred in four cases in one epidemic in the hospital. In one case it was so severe as to cause death. The stools of these infants were examined repeatedly for dysentery organisms but none was isolated. At post-mortem examination in this group a definite severe ileo-colitis—without, however, any actual ulceration—was present. This was in marked contra-distinction to the autopsy findings in the remainder of the series in which there was only a mild catarrhal change in the lower ileum in two cases. The intestine in the remaining cases appeared normal.

(6) Jaundice was present for two days before death in one case in which an autopsy was not permitted.

(7) Purpura. Two cases showed crops of purpuric spots on trunk and neck ; one of these recovered.

(8) Scurvy occurred in one case. It was discovered accidentally during convalescence when a routine X-ray examination of the long bones was made. This baby had been on the continuous intravenous saline infusion for twenty-two days. The scurvy changes shown in the skiagram were early but quite definite. Reviewing this case it was remembered that the baby had on one occasion had hæmaturia, and that for a few days he had screamed whenever his cot was approached.

Results

On considering the results I think that those of the prophylactic measures are the more striking. Since the system of isolation was established there has been no spread of infection from the four single rooms in which cases of acute gastro-enteritis were nursed to the rest of the ward. So far as can be ascertained, there has been no cross-infection between the four rooms. Moreover, since July 1937, when all suspicious cases were transferred immediately, no epidemics of gastro-enteritis have occurred in the hospital.

Of the 30 infants treated 14 recovered and 16 died, giving a mortality of 53%.

The series is too short for these figures to be of much value, but they compare favourably with the, admittedly very much larger, series recently reported from Glasgow (1937) in which the mortality for severe cases was 76%.

On the other hand, Karelitz and Schick (1931) from the Mount Sinai Hospital, New York, reported a series of 30 cases treated during a similar six months' period with a mortality of only 23%.

In conclusion I should like to thank Dr. Maitland-Jones for his help and advice and for permission to publish the report of these cases.

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Discussion.—Dr. W. W. PAYNE suggested that possibly one cause of the failure to maintain the initial improvement resulting from relieving the acute dehydration was in the nature of the fluid used for this purpose. He had found very high plasma-chloride values in infants, even when only half-strength saline-glucose was given. He suggested that frequent examination of the salt and acid-base balance of the blood might enable one to find the best fluid to use.

Dr. DONALD BATEMAN said he agreed with Dr. Wilmers, that the use of 5% glucose and saline in the drip was as effective as that of more complicated preparations. When feeding was begun, what seemed to be most important was to give the food in small amounts and to increase it very slowly. The actual type of milk preparation used did not matter much, provided the feeds were small.

It should be explained that the comparatively good results obtained by Karelitz and Schick, quoted by Dr. Wilmers, were attributable to the fact that they put their cases on a continuous drip as soon as the slightest dehydration appeared. Their series, therefore, probably contained many mild cases which would have recovered in any event, whereas this present series did not contain such cases. It must be remembered, however, that by so doing they possibly aborted some cases which would otherwise have taken a serious turn. Blood transfusion should play no part in the early treatment of a case of gastro-enteritis, but in the later stages, when hydration had been restored, a small transfusion appeared to be a great help in promoting convalescence.

A Simple Method of Preserving Breast Milk

By MARY J. WILMERS, M.D.

Seven ounces of fresh breast milk and half an ounce of sterile water are placed in an 8-oz. bottle with a sterile cork. Over the cork are placed six layers of sterile gauze, a large piece of cotton-wool, and a piece of paper, all being secured loosely with a rubber band. The bottle is placed in a Soxhlet apparatus, with cold water up to the level of milk in the bottle. The water is heated and kept at 175° F. for thirty minutes. This procedure is repeated after 24 hours, and again after 48 hours; during the intervals the bottle is kept at room temperature. The coverings of the cork are then removed, and the cork is tightened and sealed with paraffin. The milk can be kept indefinitely in a refrigerator.

This method was first used in the Infants Hospital in June, 1937.

A total of 103 pints was bottled during the period August 15, 1937, to February 15, 1938. During this period the milk was fed to 30 infants. In no case was there any untoward result. The milk was obtained almost entirely from mothers resident in the hospital.

Bacteriological examinations have been made of three samples of milk kept respectively three weeks, six weeks, and one month. These were all satisfactory, 10 c.c. of milk yielding a scanty growth of white staphylococci, and 1 c.c., 0·1 c.c., 0·01 c.c. being sterile.

Physical and chemical examination was made of a sample of milk which had been stored for three months. The physical properties were reported as being indistinguishable from those of fresh breast milk. The nitrogen and protein content were the same as those of ordinary fresh milk and the emulsification of the fat was unaltered.

An Unusual Example of Hemiplegia.—A. MAITLAND-JONES, O.B.E., M.D

Ian A., male, aged 1½ years.

History.—Admitted to the Infants Hospital 6.1.38, with left-sided hemiplegia. Three weeks previously he had begun to be very fretful and irritable ; a week later his mother noticed a purple discoloration at the outer side of the right ear and redness at the meatus of the left ear. Two days later a purple patch was noticed on the chin ; after a further two days a similar patch was seen on the left shoulder and collar-bone. During this time there was no complaint from the child although he continued to be very fretful.

Two days before admission he had fallen back unconscious while being dressed. He had vomited once, soon after the onset of this attack, and remained in a semi-conscious condition for twelve hours. On the following day the mother noticed conjugate deviation of eyes to the right and stiffness of the left arm, which the child did not use.

Past history.—Birth-weight 6 lb. 2 oz. Forceps delivery. Breast fed for three months, then put on Cow and Gate milk. Mixed diet, virol, and fruit juice, since the age of 9 months.

Family history.—No other children ; no miscarriages. Father and mother alive and well. No familial diseases.

On admission (6.1.38).—Pale, drowsy child. Very irritable when disturbed. Nutrition fair ; under-weight for age. One abrasion and two bruises on face. Two bruises on right thigh and one on left internal malleolus. Small subconjunctival hæmorrhage on right side. Chest, heart, abdomen, normal. Spleen not palpable. No head retraction or neck rigidity. Fontanelle normal. Kernig's sign negative. Marked left facial weakness and conjugate deviation of eyes to right. Pupils equal ; react to light. Discs : No papillœdema ; one small hæmorrhage in centre of left disc, and three small hæmorrhages at edges of right disc.

Weakness of left arm and leg, with some spasticity. Biceps-, knee-, and ankle-jerks active. Abdominal reflexes absent on left. Left plantar reflex extensor. Swelling over left clavicle, with discoloration of skin.

8.1.38 : The condition had deteriorated. The child was semi-comatose, with stertorous breathing, and flushed face. Complete left-sided hemiplegia. Reflexes still obtained ; left ankle clonus. The child remained in this condition for two days, after which he made a gradual, but steady, recovery.

He was transferred to the London Hospital on 20.1.38, by which time he had some movement in the left arm, full movement of the eyes, and less facial weakness. No movement of the left leg. Mental condition normal.

Progress at the London Hospital has been steady. Weakness of left arm and leg is now very slight. Movement of eyes full. No facial weakness.

Pathological investigations.—7.1.38 : Urine : No abnormality. Blood-count : Nothing significant. Platelets : 162,060 per c.mm. Bleeding time and clotting time normal.

8.1.38 : Lumbar puncture. Fluid under pressure, but of normal appearance. nothing abnormal in contents of fluid.

26.1.38 : Blood count : Nothing significant. Cerebrospinal fluid : No abnormality. Wassermann reaction negative.

Skiagrams. 12.1.38 : Old fracture, with callus of right clavicle ; recent fracture of left. No abnormality of long bones.

14.1.38 : No evidence of bone injury to skull.

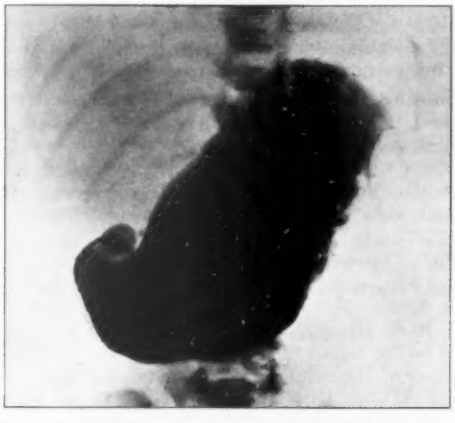
Dr. NEILL HOBHOUSE said that this case was most interesting and unusual, and could not be easily explained. To produce a complete hemiplegia, a hæmorrhage must be either deep-seated or decidedly extensive. Owing to the speed and extent of recovery in this case it was impossible that the hæmorrhage had been deep-seated; it must have been superficial and extensive. He was much surprised at the absence of convulsions, and would have expected blood to have been present in the cerebrospinal fluid. It would be interesting to know what was there now and what would happen in the future, and he hoped the child would be kept under prolonged supervision. It was quite likely that all signs of hemiplegia would clear up, and that at some future date Jacksonian attacks might occur, the nature of which would be obscure if the history was not known.

Duodenal Atresia; Gastro-enterostomy; Recovery.—K. H. TALLERMAN, M.D., and D. LEVI, M.S., F.R.C.S.

R. C., male infant, now aged 15 weeks.

Family history.—Nothing significant. First child of healthy parents.

History.—From the day after birth the child, who was breast-fed, vomited, at first immediately after feeding and later 3-4 hours after. He appeared to keep nothing down ; the vomiting was said to be projectile in character; the vomitus after a few days was of a deep yellow colour. He seemed vigorous, took his feeds well, appearing to be hungry, and passed meconium.



Skiagram taken 1½ hours after barium feed, showing hold-up in stomach and duodenum, and dilatation of the first and second parts of the duodenum.

20.11.37 : At the age of 5 days he was first seen in consultation by one of us (K. H. T.). He was obviously dehydrated, and his weight, which had been 6 lb. 12 oz. at birth, had dropped to 5 lb. 5 oz. On palpation there was a suggestion of thickening of the pylorus, but nothing definite ; no visible peristalsis and no other abnormal physical signs were observed. On the following morning (21.11.37) gastric lavage revealed a 3-oz. residue, containing bile. X-ray examination after a barium feed (screening and plate) showed a complete hold-up in the duodenum, thus

confirming the diagnosis of duodenal atresia. On this day the infant passed bile-stained material twice from the bowel. About 200 c.c. of saline were given subcutaneously during the day; the stomach was washed out, and feeds of breast milk were given.

21.11.37: Operation was carried out at 9.30 p.m. under local anæsthesia. An anterior gastro-enterostomy was performed, and the child stood the operation well. Subsequently he was given further small amounts of saline intravenously, subcutaneously, and by rectum, and was fed by mouth with small amounts of breast milk diluted with half-strength saline.

22.11.37: About twenty hours after operation, vomiting began again, and the child entered upon a peculiarly stormy period. On the next day, 23.11.37, he was bringing up bile-stained vomitus, and was keeping nothing down. He looked very ill and dehydrated. More subcutaneous saline was given.

24.11.37: On the assumption that the gastro-enterostomy was not functioning properly, the wound was reopened, a gastrostomy was performed, and a tube passed through the stoma into the jejunum. Feeding was commenced, through this tube, with 3 drm. of peptonized breast milk three-hourly. The stomach was drained by syphonage eight-hourly, and a small quantity of the bile-containing stomach contents was introduced through the tube into the jejunum. The subcutaneous administration of saline was continued. The child's general condition remained unaltered, but the vomiting was slight.

27.11.37: The tube through the stomach-wall into the jejunum was found to be loose, and bile was leaking from the wound. The tube was removed, and an attempt was made to close the fistula. For about thirty hours the stomach was drained continuously by a tube through the œsophagus. All feeding was stopped, and a continuous intravenous drip of normal saline and 5% glucose was instituted. On the next day the amount of fluid given intravenously was slowly cut down, and feeding was begun by mouth with small amounts of peptonized breast milk, at first 2 drm. three-hourly. The intravenous drip was finally discontinued on 2.12.37.

29.11.37: No vomiting; bile-containing stools being passed.

30.11.37: Bile and milk were leaking from the wound. Great trouble was experienced at this stage in holding the edges of the wound together. Further vomiting occurred from time to time, sometimes being sufficiently troublesome to make temporary omission or alteration of feeding necessary. Despite this, and the occurrence of a thrombosis at the site of the intravenous injection, the child held his own.

8.12.37: It became obvious that the abdominal wall was being digested by the stomach contents and bile, which were now pouring from the wound. No measures availed to close the fistula, but the edges of the abdominal wall were repeatedly brought together by re-suturing, with the aid of special buttons. During this time dressings of certain buffer substances were employed, to counteract the ill-effects of the escaping gastric contents; that which seemed most successful was Hartmann's solution diluted with raw egg white. An ointment composed of zinc oxide, aluminium powder, and paraffin was applied to protect the surrounding tissues.

From about 13.12.37 the child began to show definite improvement; he gained weight, and the wound began slowly to close and heal. From 1.1.38 the duration of peptonization of the breast milk was slowly lessened, and from 8.1.38 natural unaltered breast milk was given by bottle.

Blood examination (1.1.38): R.B.C. 3,400,000; Hb. 70%; C.I. 1·02; W.B.C. no abnormality. A small daily dose of iron was then commenced. The dosage was subsequently increased, and a transfusion of 50 c.c. of the father's blood was given on 11.1.38. No significant change was noted in the blood examination on 12.1.38; no abnormal red cells were seen; reticulocytes numbered 3·2%.

18.1.38 : The patient was sent home, weighing 6 lb. 15 oz., with the wound almost healed. The stools were normal, and there was no vomiting. He was now feeding from the breast three-hourly, six times daily.

Since going home he has gained steadily in weight, at the rate of about ½ lb. weekly ; the weight on 23.2.38 was 9 lb. 7¼ oz. The wound discharges only a little moisture at times, and now requires no dressing. His behaviour is in every way normal. He is contented, and sleeps well. There is no vomiting, and the bowels move normally. He is now being fed four-hourly at the breast, and is obtaining about 5 oz. at each feed. He is receiving 2½ gr. of iron and ammonium citrate thrice daily, also haliverol (commenced on 8.12.37) and orange juice daily.

Blood examination (15.2.38) : R.B.C. 4,080,000 ; Hb. 78% : C.I. 0·95. The shape, size, and colour of the corpuscles were generally good ; there was no pronounced anisocytosis, no macrocytosis, and only one normoblast could be found in a film. Examination of the white cells showed nothing significant.

Comment.—There are few records of successful gastro-enterostomy for this condition in young infants ; in the English and American literature we have found only six.

Subsequent recoveries were recorded by Steward in a baby operated on at five days of age, by Bolling on an infant aged nine days, by Abel (at eight weeks), by Higgins (at twenty-two days), and by Browne at three weeks of age. As in some of these cases the infants had lived for many days before operation, it would appear that they were suffering from duodenal stenosis rather than a true atresia. The case most comparable with the one now recorded is that operated on by Steward, but in Steward's case the patient was considerably larger on the day of operation than the child now under consideration—weighing 8½ lb. as against 5 lb. 5 oz. One of us (D. L.) has shown a similar case, that of an infant operated on at the age of 7 days.[1] This case is not, however, included in the list of recoveries set out above, because the child died at a later date, and at post-mortem examination gross abnormalities in the rotation of the gut were discovered.

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POSTSCRIPT.—The infant was last seen 26.4.38 (aged 6 months). He was perfectly healthy and normal in every way, and weighed 12 lb. 13½ oz. The operation wound had been completely healed and dry since 3.3.38.—[K. H. T.]

Infantile Myxœdema.—K. H. TALLERMAN, M.D.

S. I., female, now aged 6 years 10 months, was shown at the meeting held on 22.5.36 (*Proceedings*, 29, 1436 ; Sect. Dis. in Child., 76). She was then 2 ft. 6 in. in height, and weighed 24 lb. 10 oz. At that time she had been under treatment for less than two weeks, and her improvement was already striking. Since then she has continued to improve, and her general health has been good. In the five-month period from January to June 1937, she grew 3¼ in. in height ; on 16.6.37 she measured 3 ft. She is taking thyroid extract (B.P.) 1 gr., twice daily.

Her present height and weight are 3 ft. 2⅜ in., and 36½ lb. respectively (normal for a child of 3½ years).

Mentality : She goes to school and is in a class with children 5 years old. Although mentally she is a little behindhand she has improved enormously, especially considering that she has only attended school for one year.

[1]Proc. Roy. Soc. Med., 1936, **29**, 1213 *(Sec. Dis. in Child.*, 43*)*.

Diabetes Mellitus in Infancy.—K. H. TALLERMAN, M.D.

M. L., male infant, aged 18 months. First seen on 31.1.38, with a history of being listless for three weeks, and of drinking "pints and pints" of water. It was said that his thirst had been increasing, and that he was passing a great deal of offensive urine; also that he had lost much weight. For the previous two days his appetite had been poor; he had been drowsy, and his breathing had been deep and heavy. Neither family history nor past history revealed anything significant.

On examination.—The child showed signs of wasting, and was in a pre-comatose state. Air hunger was obvious. The urine was loaded with sugar, and there was severe ketonuria. The breath smelt strongly of acetone. He was at once admitted to hospital.

Condition on examination.—Weight: 19 lb. 10 oz. Blood-sugar: 400 mgm. per 100 c.c. He was given 20 units of insulin, and 30 grm. of glucose by mouth within an hour. Two hours later he developed symptoms of hypoglycæmia, and 170 c.c. of 10% glucose solution in saline were given intravenously within the next four hours. On the following day he was alert and bright, and, although a fair degree of glycosuria was still present, the ketosis was only slight. He was put on a diet containing 90 grm. carbohydrate, 30 grm. protein, 34 grm. fat, and, to begin with, 3 units of insulin twice daily.

The carbohydrate has now been raised to 95 grm. per day, and the insulin slowly increased to 10 units in the morning and 7 units at night. Although he is still not completely under control he has no symptoms and seems well, there is no ketosis, and he has gained more than 2 lb. in weight since admission to hospital.

Dr. W. W. PAYNE said he doubted if it was worth while, even if it was possible, to prevent the child passing a little sugar at some part of the day. In his experience it was sufficient if the child was sugar-free the greater part of the time.

Local Gigantism involving Webbed Fingers.—DAVID LEVI, F.R.C.S.

Barbara M., aged 1 year, was brought to hospital because of a congenital abnormality of the left hand, between the third and fourth fingers of which there is a thick fleshy webbing (fig. 1). These fingers, together with their nails, are enlarged. The enlargement has been present proportionately since birth. Their ventral aspects are hypertrophied and fleshy, forming a pad. The child is otherwise healthy and normal.

Family history (see pedigree table, fig. 2).—Two female relatives and one male relative on the father's side have had either webbed fingers or webbed toes. The patient is an only child.

Dr. R. W. B. ELLIS said that the gigantism might become less marked as the child grew older. A boy who had been under the care of Dr. Hugh Thursfield in the Great Ormond Street Hospital at the age of 7 had shown bilateral gigantism of the great toes associated with chondro-osteodystrophy. He (Dr. Ellis) had seen the boy again ten years later, in another hospital, and though the gigantism was still apparent (it had, in fact, been possible to identify him by his toes), the disproportion between the great toes and the others had been considerably less than in early childhood.[1]

[1] Gilford states ("The Disorders of Post-natal Growth and Development", 1911, p. 231) that syndactyly is not infrequently associated with local gigantism as in Mr. Levi's case, and Curling (*Med. Chir. Trans.*, 1845, **28**, 342) has described local gigantism of a middle finger in a patient said to come of a family in which several members had been similarly affected. He refers in the same paper to a number of examples of digital gigantism and the tendency of these enlarged fingers to become curved ulnarly.

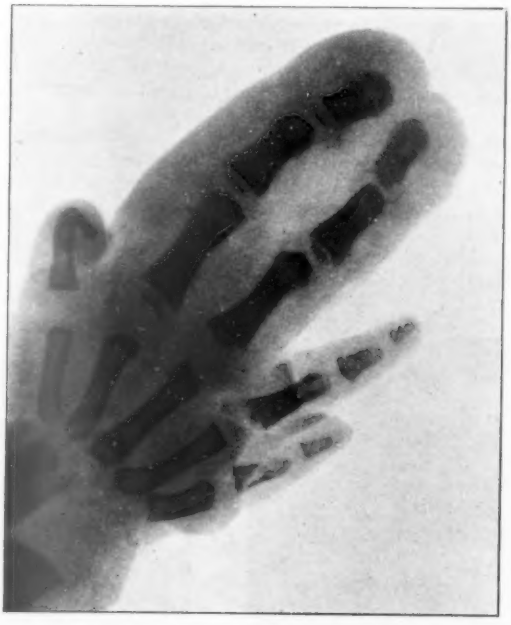


FIG. 1.—Local gigantism involving webbed fingers.

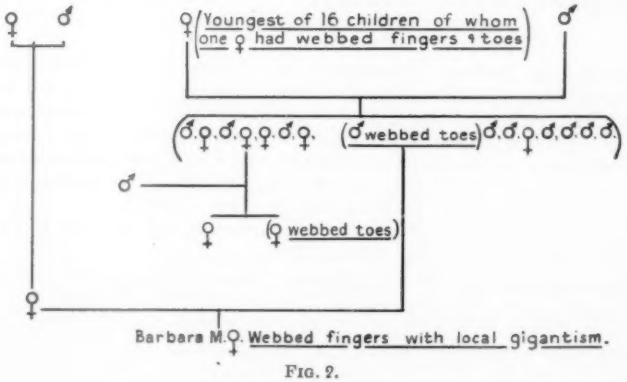


FIG. 2.

Dumb-bell Tumour: Deep X-ray Therapy—Scoliosis.—A. W. FRANKLIN, M.B., M.R.C.P. (for CHARLES HARRIS, M.D.).

Jean S., aged 11½, first seen in February 1933, when she came to hospital because of ataxia and obesity. Scarlet fever developed almost immediately, and she was sent to a fever hospital. When she returned, the muscles of the lower extremities, back, and abdomen, were completely paralysed; legs spastic; tendon reflexes increased and plantar response extensor. It was difficult to nurse her because of the gross reflex movements of the legs and the clonus produced by slight movement. Loss of sensation to superficial pain, light touch, heat and cold, and deep pain was complete to level of xiphisternum and partial above that level up to the nipples. Lumbar puncture (May 1933) yielded a clear fluid; lymphocytes 6 per c.mm.; protein 200 mgm. %; chlorides 725 mgm. %. Wassermann reaction negative. At about this time signs of consolidation were observed in the upper part of the left side of the chest. Diagnosis: Compression of spinal cord at level of 5th thoracic segment; probably in association with an intrathoracic tumour.

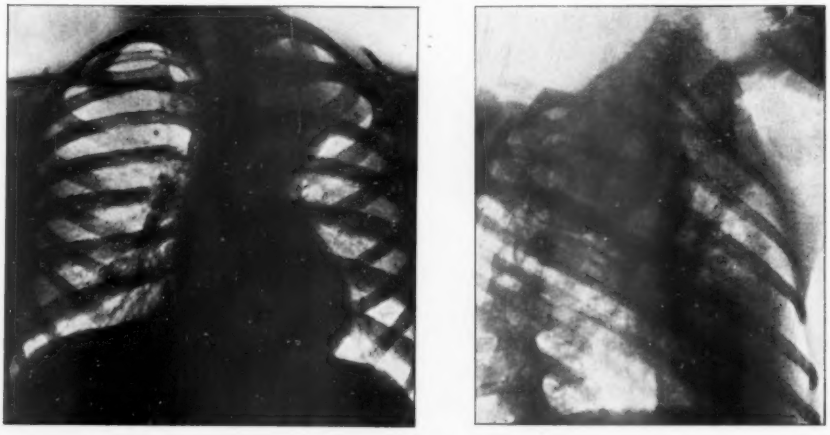


FIG. 1.—Skiagrams of chest taken 6.12.35.

Operation (6.6.33, Professor Paterson Ross).—Laminectomy of 1st to 6th thoracic vertebræ. A whitish tumour was found overlying the spinal cord for the whole length exposed, but not extending beyond the operation site. The tumour compressed the right side of the spinal cord and extended round and involved the nerve-roots; it was too vascular to be removed by excision. As much as possible was removed by diathermy. Tentative diagnosis of fibrosarcoma made on microscopic examination (fig. 2).

After the operation the patient quickly recovered the use of her leg and back muscles. The plantar responses became flexor and during the next four months full sensation returned over the area affected. Soon after the decompression of the spinal cord, deep X-ray therapy was instituted over the intrathoracic tumour, and was continued during June and July 1933. A further course lasting a month was given during October and November 1933; since that time the child has continued to have full use of her legs. No further sensory changes have been detected. The only remaining abnormality is the rather brisk tendon reflex. The size of the tumour has not materially altered since the end of 1933 (fig. 1). The patient suffers from anorexia

occasionally but does not cough. She has continued to gain weight rather in excess of the average.

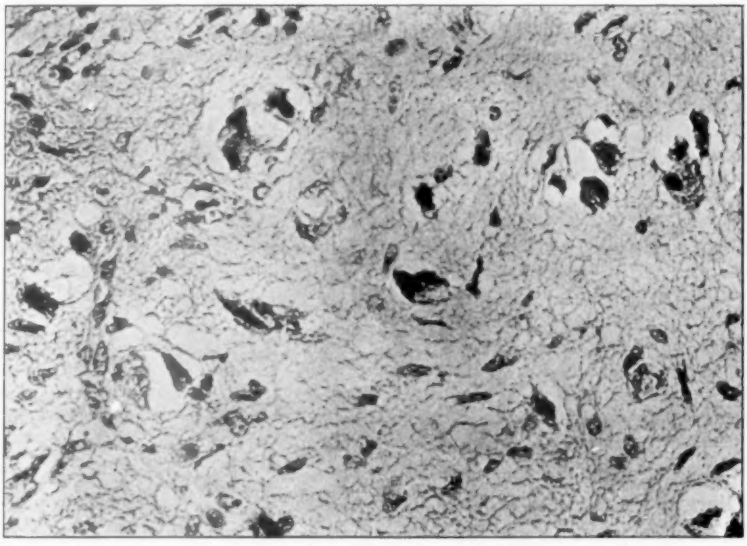


FIG. 2.—Photomicrograph of a section of the tumour removed from the surface of the spinal cord.

For the past three years there has been increasing distortion of the chest, apparently due to scoliosis of the thoracic vertebræ. It is suggested that this distortion has been brought about by the deep X-ray therapy rather than by either the laminectomy or the intrathoracic tumour.

Pyloric Stenosis in an Infant aged Five Months.—CHARLES HARRIS, M.D.

Eileen R. was brought to hospital at the age of 5½ months, having had projectile vomiting for two months. She continued to vomit in hospital. There was visible peristalsis, and a swelling, resembling an enlarged pylorus, was felt.

Rammstedt's operation was carried out by Mr. David Levi two days after the infant's admission to hospital. She made an uneventful recovery and has since been free from symptoms.

At operation marked hypertrophy of the stomach was found and a hyperplastic sphincter, which was divided in the usual way.

Green Teeth following Icterus Gravis.—R. W. B. ELLIS, M.D.

G. C., a boy aged 2½ years, born at term of normal parents. Four older children well; one died, aged 13 days, from cerebral hæmorrhage. No family history of icterus or œdema. The child was noticed to be jaundiced eight hours after birth; the jaundice deepened in intensity during the first week. During this time he had had six intramuscular injections of maternal blood, and at the age of 7 days he was admitted to the Infants Hospital. At this time he was deeply jaundiced, the skin

being olive green ; the liver and spleen were both enlarged. The fæces were greenish-yellow ; bile was present in the urine. The infant was drowsy and unwilling to suck. The temperature was 102° F. on admission, falling to normal in two days.

Blood examination (on admission) : R.B.C. 990,000 ; Hb. less than 15%. W.B.C. 35,000 ; polys. 36% ; eosinos. 5·2% ; hyals. 5·6% ; lymphos. 38·6% ; blast cells 8·4% ; myeloblasts 6·0. Normoblasts 55,110 per million R.B.C. ; megaloblasts 198,000 per million R.B.C.

Wassermann reaction (both parents and infant) negative.

The infant was given two blood transfusions, and ferri et ammon. cit., gr. v t.d.s. There was rapid improvement. He was discharged after ten weeks still slightly jaundiced. The jaundice had cleared at the age of 12 weeks, since when he has been well.

The upper incisors erupted when he was 6 months old, and were olive green in colour. He now has 20 teeth, all of which are partially green. The upper central incisors are completely green, but the other fully erupted teeth show a sharp line of demarcation between the distal part of the tooth which is green, and the proximal part which is of normal colour.

Comment.—This is a rare but recognized sequela of icterus gravis neonatorum, the colour of the teeth being presumably due to icteric staining of the membrane during the first weeks of life. It is clear that the first teeth to calcify and erupt (the upper central incisors) are those most completely coloured, whereas those which developed later have only the crown or cusps affected.

Allergic Purpura.—R. W. B. Ellis, M.D.

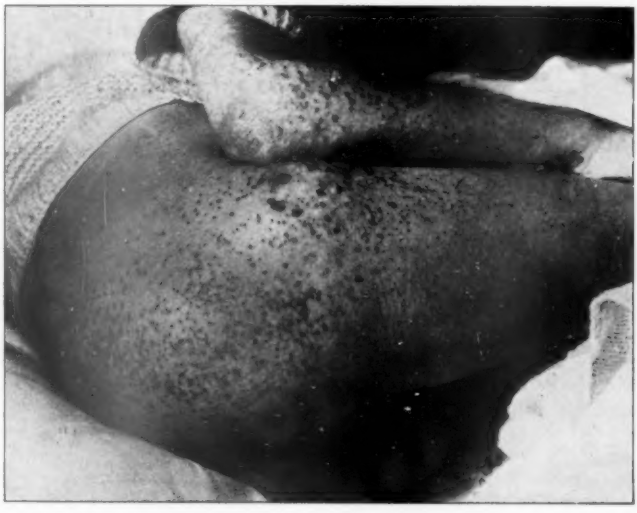
E. M., a boy aged 9 years. Father died of rheumatic carditis. Family history of gout, but none of allergic or hæmorrhagic disease. Patient was well, except for measles and mumps, until August 1937 when he complained of pain and swelling of right foot and ankle. This was followed by swelling and limitation of movement of both knees. A number of large urticarial wheals subsequently appeared over both tibiæ, subsiding in two days, but being replaced by crops of purpuric lesions. Swellings then appeared on the forearms and wrists, and a large œdematous swelling in the region of the left elbow. These again were followed by numerous purpuric lesions. The child began to vomit and was admitted to Ramsgate Hospital in September 1937. He was there found to have numerous purpuric lesions on trunk and limbs, and a severe sore throat (the swab giving a pure growth of hæmolytic streptococci). The vomiting continued for three weeks, and on one occasion there was hæmatemesis. Blood then appeared in fæces and urine. He had recurrent abdominal pain. After repeated injections of intramuscular blood and calcium gluconate by mouth he was transferred to Guy's Hospital on 22.11.37.

On examination.—At that time he was extremely pale, with several indurated masses ½ in. in diameter over the forearms, and many purpuric lesions, which appeared as small urticarial wheals with hæmorrhage into them, over the legs, buttocks, and forearms. The tip of the spleen was just palpable at the costal margin, and there were several enlarged glands in the groins. The apex beat was forcible, ¼ in. outside the nipple line ; there was a soft systolic murmur in the mitral area. The tonsils were obviously infected. Both urine and fæces contained blood in considerable amount. The tourniquet test was negative, and has been so on several occasions.

Since this time, the hæmaturia has persisted almost continuously, though lessening during the last ten days since the boy has been on Blum's No. 1 diet. The fæces became free from blood shortly after admission. He has been transfused four times (November 27 and December 4, 15, and 30) ; there has been a temporary increase in the hæmaturia (though no hæmoglobinuria) following each transfusion.

On December 9 there was a recurrence of the sore throat, and on December 13 a sudden and gross œdematous swelling of the right face occurred, principally affecting the eyelids, and having the appearance of angioneurotic œdema. This subsided in two days.

At the present time the general condition is improved; there are only very few raised purpuric lesions, but hæmaturia is still present.



Allergic purpura. Showing association of purpuric and urticarial lesions.

Investigations.—Radiological examination: Chest, abdomen, and renal tract (pyelograms) normal.

Fæces: No ova or parasites found on repeated examination. Cultures gave growth of *B. coli.*

Antistreptolysin titration (urine):

12.1.38: 80 units } within normal range.
28.1.38: 50 units }

Urine: 23.11.37: Blood present; albumin present in excess of blood. Numerous red blood-cells; no pus cells. 8.1.38: Deposit contains fresh unlaked red blood-cells and corresponding number of white blood-cells. A small number of casts present, mainly hyaline. No bacteria seen. Cultures sterile. Streptococci as such are evidently *not* being passed in the urine. 17.1.38: Albumin 0·5%. Many red blood-cells. No hæmoglobinuria. Occasional pus cells. 4.2.38: Contains red blood-cells and slight excess albumin.

Cultures from throat swabs. 29.11.37: Growth of *Staphylococcus albus* and *Streptococcus viridans.*

10.12.37: A mixed fairly heavy growth of *Streptococcus hæmolyticus, M. catarrhalis,* and Gram-negative bacilli of the hæmophilic group.

13.1.38: Cultures from both tonsils give very strong growths of hæmolytic streptococci, Group A (pathogenic variety).

Blood examination (23.11.37): Bleeding time normal. Clotting time 1 min. 20 sec.

	23.11.37		4.2.38
R.B.C. ...	2,980,000	...	3,500,000
Hb.	48%	...	54%
C.I.	0·8	...	0·8
W.B.C. ...	11,000	...	10,000
Polys. ...	57%	...	56%
Eosinos. ...	18%	...	8%
Lymphos. ...	22·5%	...	32%
Hyals. ...	2·5%	...	4%
Reticulocytes	1·5%	...	Very low
Nucl. reds ...	None seen	...	None seen
Platelets ...	250,000	...	350,000

21.2.38: Mantoux test, 1 : 1,000, negative. Intradermal test with hæmolytic streptococcal toxin 1 : 250, strongly positive.

Platelets 308,000 per c.mm. Bleeding time 7 minutes 20 seconds (prolonged). Clotting time 2 minutes 50 seconds.

Comment.—This child shows an unusually clear association of allergic phenomena, purpura, and hæmorrhage from the gut and urinary tract. The first are represented by joint swellings, urticaria (appearing as separate lesions and also as wheals with hæmorrhage into them), angioneurotic œdema, and marked eosinophilia. It is probable that the positive skin reaction to hæmolytic streptococcal toxin is significant in this respect. I am inclined to regard the tonsils (from which hæmolytic streptococci have been cultured several times) as the exciting if not the primary cause of the hæmorrhagic condition. Now that the hæmaturia has ceased for some days, I think that the tonsils should be removed, even at the risk of a temporary recurrence of hæmorrhage. The condition, however, differs from that commonly seen in purpura due to streptococcal infection, in that the platelets are not reduced, the tourniquet test is negative, and the bleeding time has only recently become prolonged.

Dr. A. G. WATKINS said that about a year ago he had seen a girl aged 10 years, who had a rash similar to that in Dr. Ellis's case, showing the same type of purpuric and urticarial lesions, accompanied by joint and abdominal pains. The history was that the rash had come out following the eating of a pomegranate. The child was admitted to hospital and after the rash had disappeared a pomegranate was given to her and the rash appeared again. An intradermal test to pomegranate was prepared and this gave a positive skin reaction.

A hæmaturia developed and persisted for nearly four months, but eventually cleared up, and when the child was seen about a year later there had been no recurrence of the rash and the urine was normal.

Gargoylism.—R. W. B. ELLIS, M.D.

D. S., a girl, aged 1 year 8 months, was brought to hospital in February 1938, on account of mental retardation. This is thought to date from earliest infancy, the baby having been consistently difficult to feed and refusing the breast. She can now sit up alone but makes no attempt to stand or crawl, feed herself, speak, or control excretions. She is chronically constipated.

The parents are unrelated and normal. A maternal great uncle was in an asylum.

On examination.—A mentally defective, fretful child, with a peculiarly raucous cry. Temperature 99° F., pulse 110, respirations 20. She has the characteristic "gargoyle" facies, with heavy features, depressed nasal bridge, hyperteleorism, and coarse dark eyebrows (figs. 1 and 2). Bilateral clouding of the corneæ. Profuse purulent nasal discharge. Ten teeth present. The hair is fair and coarse, being of almost exactly the same shade as that in the majority of cases of this kind previously seen. The skull appears hydrocephalic with considerable frontal bulging; anterior fontanelle

$1\frac{1}{8}$ inches in diameter. Circumference of skull $19\frac{7}{8}$ inches. Intermeatal diameter (over vertex) $13\frac{3}{8}$ inches. The distended frontal veins lie in gutters in the frontal bones. There is some ridging of the skull posteriorly. The ears are set very low, and the lobes deflected forward. The thyroid is not palpable. Limbs: Limitation of extension at shoulders and elbows and of extension and abduction at hips. The hands show the characteristic fixed flexion deformity of the fingers. Coarse fair hair is present over the back and arms. There is a moderate degree of dorsilumbar kyphosis. Chest: Circumference $20\frac{1}{8}$ inches; slight flaring of lower ribs. Abdomen: Circumference 21 inches. Ventral hernia. Liver enlarged 2 finger-breadths and spleen 1 fingerbreadth below costal margin.

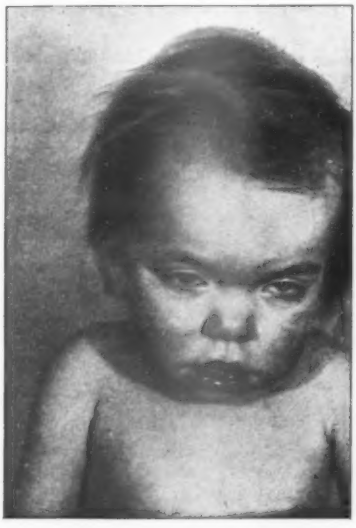


FIG. 1.—Gargoylism. Showing heavy features, coarse dark eyebrows, and hyperteleorism.

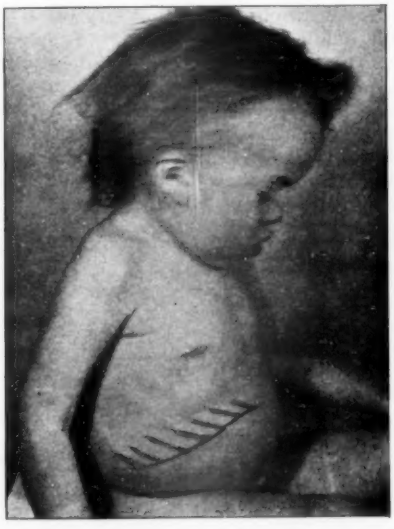


FIG. 2.—Gargoylism. Showing hydrocephalic skull, low-set ears, hepatomegaly, and ventral hernia.

Radiological examination: The changes in the long bones are less marked than in previously reported cases, but the bones of the upper extremity are thicker and broader than normal, and there is bilaterally some irregularity of the head of the humerus and glenoid fossa. The metacarpals and phalanges show more characteristic changes of chondro-osteo-dystrophy. Both acetabula are poorly developed, and lack the upper lip. The bodies of the lumbar vertebræ, particularly the first and second, show a tendency to the "sabot-shape" seen in previous cases, and lack the notched appearance normal at this age.

Pituitary fossa: Not enlarged. Posterior clinoid processes appear deformed and directed backward.

Blood examination: R.B.C. 4,400,000; Hb. 78%; C.I. 0·9. W.B.C. 11,000 (polys. 36%; lymphos. 56%; hyals. 6·5%; metamyelos. 1·5%). Platelets 200,000 per c.mm. Reticulocytes 1%. Blood cholesterol: 296 mgm. per 100 c.c.

Wassermann reaction negative.

Ophthalmic report (Mr. F. W. Law): "Lack of co-operation entirely precluded slit-lamp examination of the corneæ. Indeed all examination was actively resisted, but none the less a thorough examination with the loupe was possible. The corneæ

show a generalized haze which is in my opinion present throughout its substance. The clinical appearance closely resembles that seen in buphthalmia, when it is due presumably to the raised tension. There were no visible vessels present and it is likely that the haze is due to a generalized fibrosis, possibly complicated by separation of the corneal lamellæ."

Cerebrospinal fluid: Pressure 120 mm. Clear colourless clot-free fluid; no cells seen. Chlorides 760 mgm. per 100 c.c.; protein 70 mgm. per 100 c.c. Sugar normal; globulin test negative; cultures sterile.

Comment.—This child shows the characteristic features of gargoylism (facies, mental deficiency, cranial deformity, corneal opacities, hepatosplenomegaly, kyphosis, &c.), and the bone changes, though not marked or universal, are those of chondro-osteo-dystrophy. The pituitary fossa, however, does not show the enlargement seen in a number of other cases.

The question has been raised as to the possible relationship of this syndrome to hypothyroidism. Two autopsies by Stewart [1] certainly indicate that gargoyles may show thyroid degeneration, although little, if any, improvement is observed with thyroid treatment. However, the facies, cranial deformity, lipoid degeneration of the brain, and other features are quite distinct from those seen in primary hypothyroidism, though Evans [2] recently pointed out that the hooked lumbar vertebra commonly present in gargoylism may also be seen in cases of hypothyroidism, and I have seen it in two typical cretins whose general condition and mentality responded well to thyroid treatment.

In view of the histological appearance of the brain, which resembles that in juvenile amaurotic idiocy, it has been suggested that gargoylism may prove to be allied to the lipoidoses. Ashby *et al.* [1] are inclined to accept this view. Recent biopsy examination [3] of the liver and spleen in a case showing hepatosplenomegaly showed, however, no lipoid infiltration of these organs, so that at present the evidence is inconclusive.

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Postscript.—An encephalogram (50 c.c. air injected) shows generalized dilatation of the ventricles, and the situation of the air present over the cortex suggests multiple areas of cortical atrophy, the largest of these being over the frontal pole (Plate I).

Massive Collapse of Lung following Tonsillectomy. Recovery.—R. W. B. Ellis, M.D.

J. B., a girl aged 9, had had asthmatic attacks occurring about every six weeks, between the ages of 3 and 8 years. After treatment with breathing exercises, &c., she had been discharged as cured in November 1936 and has had no further attacks. Normal infancy. Family history negative.

In December 1936 she was seen suffering from follicular tonsillitis, and subsequently complained of sore throats several times. A skiagram of the antra showed bilateral opacity in lower parts, suggesting infection. She was admitted to hospital for tonsillectomy on 4.4.37. Physical examination at that time showed a grossly infected right tonsil and mucopus under the left middle turbinate. No other abnormality. Skiagram of chest (12.4.37) showed well-marked root shadows only.

14.4.37: Tonsillectomy was performed under general anæsthesia, and lipiodol injected into the maxillary antra. The operation was apparently carried out uneventfully, and bleeding was not excessive.

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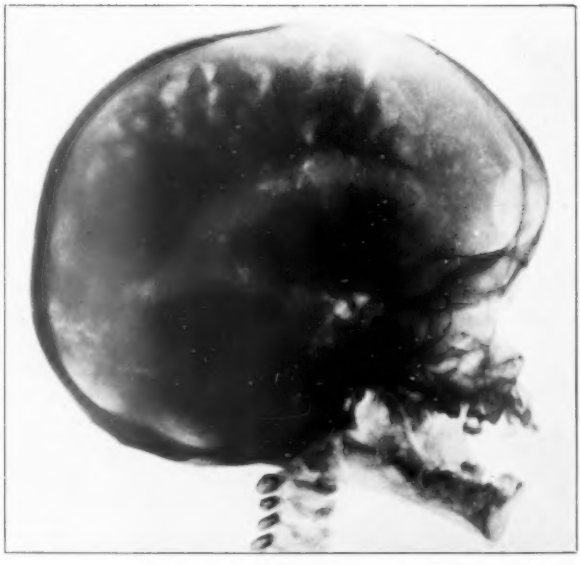
Section for the Study of Disease in Children.

PLATE I.



Encephalogram showing gross dilatation of ventricles and cortical atrophy.

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PLATE II.

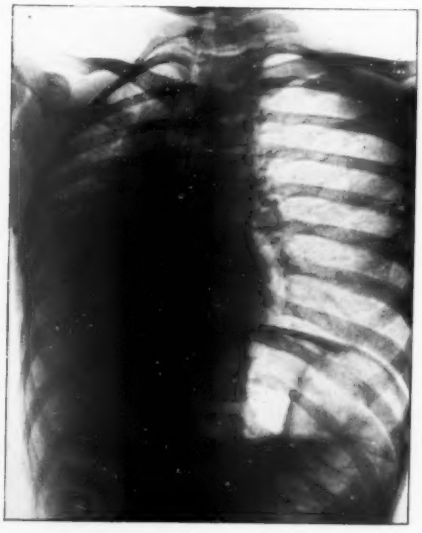

FIG. 1.—17.4.37. Massive collapse of right lung. Trachea, heart, and mediastinum, displaced to right.

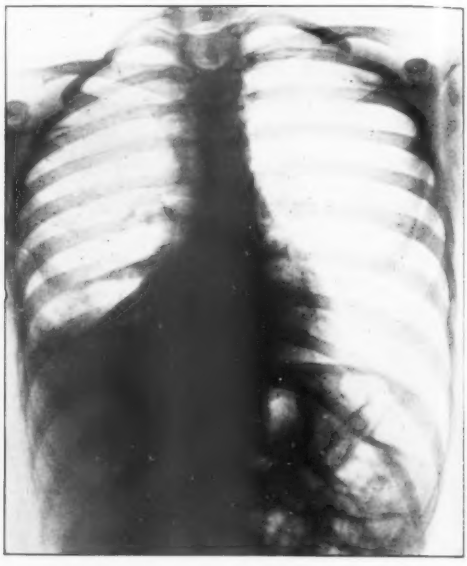

FIG. 2.—19.4.37. Partial re-expansion. Right lower lobe still collapsed.

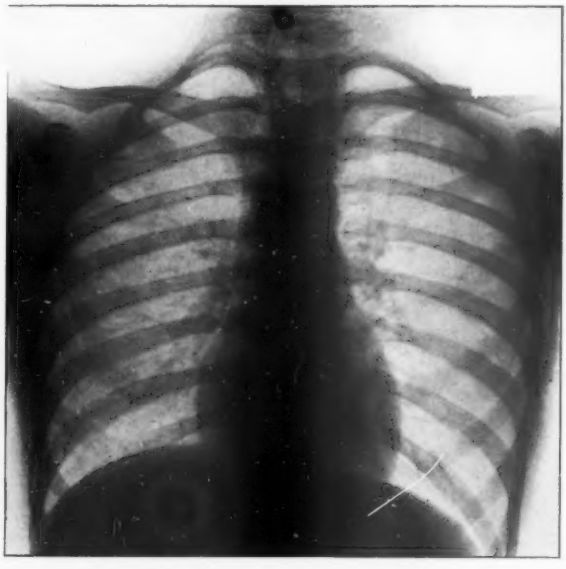

FIG. 3.—26.4.37. Complete re-expansion.

R. W. B. ELLIS: Massive Collapse of Lung following Tonsillectomy. Recovery.

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PLATE III.

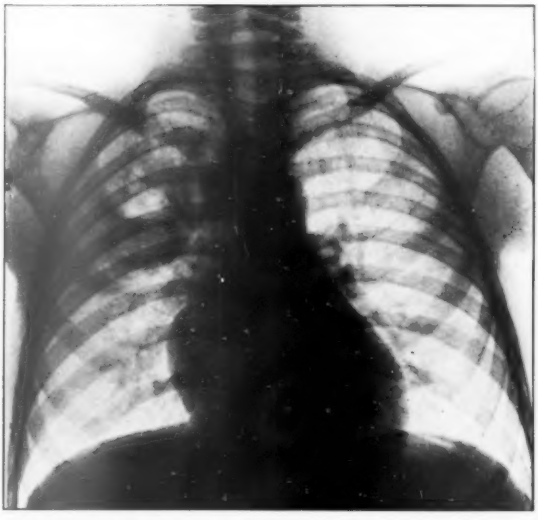

FIG. 1.—17.7.37. (Upright.) Lung abscess. Right upper zone, showing fluid level.

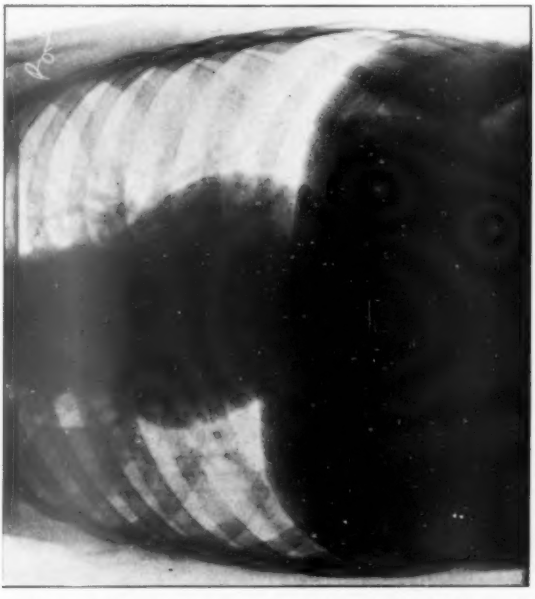

FIG. 2.—17.7.37. (Horizontal.) Showing fluid level (patient lying on right side).

R. W. B. ELLIS: Lung Abscess following Tonsillectomy. Recovery.

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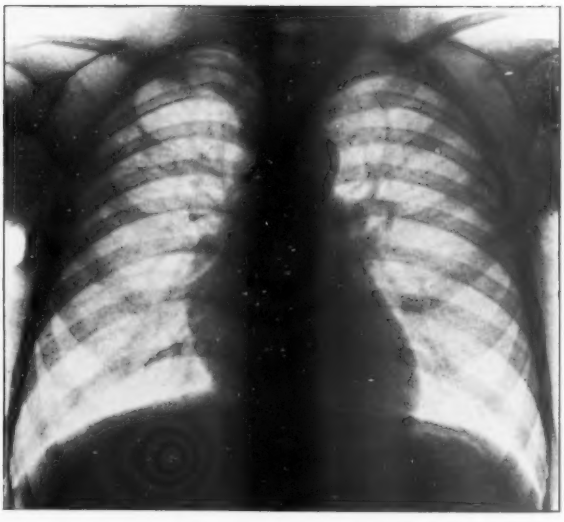
PLATE IV.



11.1.38. Right lung clear.

15.4.37 : The temperature had risen to 102° F. and the pulse to 140. Respiration 30. The child appeared acutely ill. There was displacement of the heart to the right (the apex beat not being palpable to the left of the sternum). The movement of the right chest was diminished, and there was dullness to percussion to the level of the 3rd rib on the right. Breath sounds were almost completely absent over the right lung except in a small area at the right apex, where they were diminished.

The physical signs, temperature, and pulse remained unchanged for three days, when the general condition improved. The child was given inhalations of 7% carbon dioxide in oxygen from 16.4.37 to 21.4.37, for five minutes hourly during the day, and breathing exercises.

19.4.37 : The dullness of the right chest had considerably diminished in extent, being confined to the base, and the apex beat was palpable an inch within the left nipple line. 24.4.37 : The dullness and diminished air-entry at the right base were no longer detectable ; the apex beat was in normal position.

29.4.37 : Discharged ; well ; free from physical signs. Since this time she has remained well, except for occasional cough, and now shows no abnormality.

Radiological examinations. 17.4.37 (Plate II, fig. 1) : Massive collapse of right lung, with displacement of heart and mediastinum to right. Small area of translucency at right apex. 19.4.37 (Plate II, fig. 2) : Collapse of right lower lobe, seen as triangular shadow obscuring right cardiophrenic angle. Re-expansion of upper and middle lobe. Displacement of heart less than on 17.4.37. 26.4.37 (Plate II, fig. 3) : Re-expansion of right lung. Heart position normal. Subsequent skiagrams have shown no change.

Lung Abscess following Tonsillectomy ; Recovery.—R. W. B. Ellis, M.D.

K. B., a boy, aged 8, was admitted to Guy's Hospital on 12.6.37, on account of general debility, and cough and sore throats for the past twelve months. Acute tonsillitis February 1937. Scarlet fever at 4 and measles at 5 years. Father died from nephritis ; mother well. Three sibs living ; one died of pneumonia and one of volvulus.

On examination (12.6.37).—A pale, poorly nourished child ; no cyanosis or clubbing. Slightly diminished air entry right base, with râles inner border both scapulæ. Tonsils infected. X-ray examination showed enlargement of right hilar shadow. Mantoux test (1 : 10,000 and 1 : 1,000) negative. Stomach washings negative for tubercle bacilli.

24.6.37 : Four teeth extracted under ethyl chloride.

29.6.37 : Tonsillectomy performed (ethyl chloride and ether) and a fifth tooth extracted. The right tonsil was removed without difficulty, but there was much hæmorrhage from the left. Patient subsequently vomited 6 oz. blood. Cultures of tonsils gave a heavy growth of hæmolytic streptococci. 4.7.37 : Secondary hæmorrhage (4 oz.) from left tonsillar fossa, controlled with difficulty.

The patient was in fair general condition until 11.7.37 (twelve days after operation), his temperature not rising above 100° F. He then had sudden pyrexia (104° F.) and began to cough persistently ; fine râles were present in the right middle zone. During the following week, he began to bring up large amounts of green, foul-smelling sputum, and showed physical signs of consolidation in the right middle zone. Temperature swinging daily to 103° F. Prontosil gr. 7½ t.d.s. was given and postural drainage was carried out. Bacteriological examination of sputum showed occasional spirochætes and fusiform bacilli. The temperature gradually settled, and after remaining unchanged for ten days, the physical signs slowly cleared. The child was discharged to a convalescent home on August 12, practically free from cough and sputum. Whilst there, he developed diphtheria, and when seen in October 1937 he

was suffering from pains in the legs, tachycardia, and debility, but showed no signs of pulmonary disease. He was readmitted to hospital for three weeks; since readmission he has been in poor general condition but free from cough and sputum.

Radiological examinations. 10.6.37 (before tonsillectomy): Enlargement of right hilar shadow. 12.7.37: Dense opacity right middle zone. 17.7.37: Cavity in centre of opacity in right lung, showing shifting fluid level in upright and horizontal positions. (Plate III, figs. 1 and 2.) 29.10.37: Gland at right root. 5.1.38: Median opacity normal. Diaphragm moves evenly and well. Costophrenic angles clear. Well-marked roots only. 11.1.38: Right lung clear (Plate IV).

Comment.—In both these cases the conditions followed tonsillectomy. In the first case (massive collapse of lung) the operation had apparently been carried out uneventfully, but in the second it is not improbable that the child inhaled a small fragment of tonsil during the operation, or septic material subsequently when there was secondary hæmorrhage. In both cases, after considerable discussion, it was decided not to carry out bronchoscopy—in the first case because the collapsed lung began to re-expand rapidly under treatment by breathing exercises and inhalation of carbon dioxide, and in the second case because the lung abscess was draining freely. It was of great interest to see how rapidly both the abscess and the consolidation around it disappeared, subsequent skiagrams showing an apparently normal lung.

Bilateral Hydrarthrosis of Knees.—R. A. MILLER, M.B.

Rita H., aged 5 years, admitted to the Infants Hospital 22.7.37 with a history of swelling of both knees for nine weeks. There was no pain in the joints but there was discomfort on flexing the knees. About two weeks before admission she had had an illness suggestive of dysentery.

Family history.—Five children in family. The first died of pneumonia aged 4 months; the second, aged 10 years, is alive and well; the third is the patient; the fourth, a premature child, died aged 3 days; the fifth, aged 2 years, is alive and well. Mother and father alive and well. The mother's Wassermann reaction is positive.

On examination.—General condition moderately good. No stigmata of congenital syphilis, but liver and spleen enlarged. Both knees showed painless hydrarthrosis, with full range of movement in the joints.

Investigations.—Mantoux reaction negative. Wassermann reaction strongly positive. Skiagram of knees showed no bony changes.

Progress.—After three days in hospital the child developed measles and had to be transferred to a fever hospital. On her return, on 26.2.38, she was found to have interstitial keratitis in addition to the previous signs.

Section of Obstetrics and Gynæcology

President—MILES PHILLIPS, M.D.

[*November* 19, 1937]

DISCUSSION ON THE SURVEY OF MATERNITY WORK IN L.C.C. HOSPITALS 1931-1936 [Dr. LETITIA FAIRFIELD][1]

Professor Munro Kerr: Before we proceed to discuss this interesting communication we must be quite clear regarding what we are actually considering. We are discussing the 292 deaths from "truly obstetric causes" in a series of 79,254 confinements. Excluded from the series are 19,202 cases of abortion with 248 deaths; and 743 cases of ectopic pregnancy with 43 deaths. Now as the Registrar-General includes in his returns of deaths directly due to pregnancy and childbirth, all deaths from abortion and ectopic pregnancy, comparison between the results in the London County Council (L.C.C.) Hospitals, as presented by Dr. Fairfield, and those for the country generally, cannot be made. Neither is it possible to make comparisons between the results in the large voluntary Maternity Hospitals of Edinburgh, Glasgow, Manchester, Liverpool, Sheffield, Newcastle, and the L.C.C. Hospitals, because in the former anything from 20–60% of the cases are "non-booked" and emergencies, whereas we are informed that in the latter less than 10% (9·1% in point of fact) are non-booked and have not attended the L.C.C. antenatal clinics. Lastly, as only a few lines are devoted to deaths from "associated causes", the report boils down to deaths directly due to pregnancy and childbirth, with abortion and ectopic pregnancy excluded.

In the 79,254 confinements (live and stillbirths included) the death-rate has fallen from 5·08 per 1,000 in 1931, to 2·51 in 1936, and it is further stated "that for the ten months of 1937 although the general London rate is 15%–20% higher than for 1936 the mortality rate in the L.C.C. hospitals has fallen by over 20%". That is to say it has been reduced to 2 per 1,000 (abortions excluded). This figure, we must all agree, is highly satisfactory.

As the death-rate from sepsis for 1936, which I will consider later, is 1·19 per 1,000 we get 1·32 per 1,000 for deaths due to "causes other than sepsis". Now this is the group in which operative technique, or handling, plays so important a role. The reduction of maternal mortality in the L.C.C. hospitals has been especially striking in the reduction of the deaths from "causes other than sepsis". We see the conservatism practised in the forceps rate—3·3% of births on an average. This compares with the 2·5%–2·7% rates for the East End Maternity Hospital and the General

[1] *Proceedings*, 1938, **31**, 237 (Sect. Obst. and Gyn., 1).

Lying-In Hospital, York Road, whose all-in death-rate has been particularly low for many years; it must always be remembered, however, that in quoting their results the number of " emergencies " admitted is negligible.

The sepsis death-rate has been reduced from 2 per 1,000 in 1931 to 1·19 in 1936. It must be remembered, however, that deaths from abortions are not included and they account for 20% of the deaths from sepsis in the country generally.

If and when we get down to the region of 1 per 1,000 (abortions included) or 0·8 per 1,000 (abortions excluded) we are approaching the irreducible minimum for sepsis. There always occur odd cases in which sepsis develops, and that leads me to take exception to a very common statement, and one expressed by Dr. Fairfield, namely, that auto-infection is of comparative unimportance. As a matter of fact, as shown by the figures quoted by Smith (Aberdeen), localized infection in or on the patient's person is responsible for fully 30% of grave infections; and for even a larger proportion of mild infections. We should be able to cut down, almost completely, *extrinsic* infection, by masks, gloves, isolation of infected patients, attendants and visitors, proper admission of patients, limiting the number of beds in wards, improving the design and layout of the labour-room, section, &c. Some figures presented by Dr. Fairfield demonstrate how well extrinsic infection has been combated. But to reduce *intrinsic* infection to a proportional extent is very difficult indeed. I specially stress this point and would ask all engaged in the practice of obstetrics to reconsider the question of intrinsic infection as here defined.

The figures presented for the eclampsia group may at first sight appear a little disappointing, but there is no cause to be depressed unduly. In the 41,430 confinements in 1934–36—in all of which the patients received ante-natal care—there were 34 cases of eclampsia with six deaths. This, of course, is a relatively high death-rate but not an unduly high incidence when it is taken into consideration that two patients refused to co-operate. Three were of the " fulminating " type—a particularly virulent form as we all know; in my opinion this type should be treated immediately by Cæsarean section—medical treatment gives most disappointing results.

There is not the slightest question that the more complete the ante-natal care the lower is the incidence of eclampsia—and Dr. Fairfield's figures prove this. It is hardly likely, however, that even when our knowledge of the ætiology and prevention of eclampsia is more complete, we will ever be able entirely to eliminate eclampsia as a possible complication of pregnancy or labour.

Hyperemesis is in a different category, except the grave hyperemesis of the later months. The ordinary hyperemesis of the earlier months can almost always be arrested unless the patient has been permitted to drift into an extremely critical condition.

The results with regard to accidental hæmorrhage are excellent. The same applies to placenta prævia. Among the women who attended the antenatal clinics of the L.C.C. there was only one death from placenta prævia. Cæsarean section in all but the simplest varieties is the ideal treatment and it should be noted that among the 87 cases in which Cæsarean section was performed there were only two deaths.

Less satisfactory, possibly, are the results in the groups including post-partum hæmorrhage, retained placenta, shock, and rupture of the uterus.

Most of the fatalities from post-partum hæmorrhage occurred in women gravely ill from anæmia, heart disease, albuminuria, &c. In the last 16,000 cases there was no death from post-partum hæmorrhage.

The treatment of the retained placenta in a woman who has lost a large quantity of blood is rightly stressed as being a complication requiring great skill and judgment —to remove the placenta immediately may not always be the best procedure. It will be noticed that as regards adherent placenta there was only one example of a pathological densely adherent placenta in the 79,254 cases. Placenta accreta is, in my experience, an extremely rare complication.

I know of no problem in obstetrics at the moment more deserving of serious investigation than obstetric shock. Odd deaths from shock occur from no apparent reason and most unexpectedly. I would here stress the importance of bringing into hospital for her confinement the multipara in indifferent health and tired out by domestic duties. The majority of the examples of ruptured uterus referred to in the paper were the result of bad obstetrics, but in few of the number could blame be attached to the staffs of the hospitals.

The Cæsarean sections (Table XIIIa in the report) make a good showing. The percentage to the total confinements has fallen in recent years—0·76% for 1935 and 0·85% for 1936. This rate I do not think unduly high for the type of work the L.C.C. hospitals are engaged in undertaking. The all-in death-rate (every condition included) was 1·3 in 1936—in previous years it had been four or five times higher. Further, in 1936, in a series of 76 cases of pelvic deformity there was no death, and in 36 cases of placenta prævia there was no death.

The results presented in the paper demonstrate beyond question what can be accomplished by good obstetrics. This is probably most strikingly evidenced by the marked improvement in the results from year to year, and we congratulate the staffs of the L.C.C. hospitals on what has been achieved.

Other matters referred to such as size, design, and lay-out, of maternity units and the staffing arrangements, call for most serious consideration at the present time, when so many local authorities are proposing to erect additional hospitals to cope with the ever-increasing demand for institutional treatment, but time does not permit me to discuss them.

Professor James Young said that the record which Dr. Fairfield had presented must be regarded as a remarkable one. The fact that the maternal death-rate in the L.C.C. maternity units had been reduced by 50% during the six years 1931–1936 was a tribute both to the wisdom of the Local Government Act of 1929 and to the efficiency with which the L.C.C. had undertaken the huge maternity responsibilities which that Act implied. Dr. Fairfield's record had an important bearing upon a subject of acute controversy at the present time, both in administrative and medical circles. That was the relative safety of hospital—as contrasted with domiciliary—midwifery. About ten years ago he (Professor Young) had estimated from the data available at that time that a woman ran about a six times greater risk of dying from puerperal sepsis in our large central hospitals, than if she was delivered in her home. The major risk in hospital had always been epidemic contagion amongst normal cases. This risk, as Dr. Fairfield had shown, had been practically eliminated in the large L.C.C. practice. There could be no doubt that this increased safety had been in the main due to the recognition of the potential danger of the throat-and-nose carrier of the type of hæmolytic streptococcus responsible for the major types of sepsis.

The work of the Colebrooks had for the first time provided data upon which a sound system of practice could be based. He (Professor Young) agreed with Dr. Fairfield that in the maternity unit repeated bacteriological swabbings and other laboratory procedures were of relatively small importance compared with a rigid ritual in regard to every detail in the routine daily technique. The throat swabbings so vigorously practised in some clinics were in the main to be regarded merely as evidence of a breakdown in these important details. The segregation of all suspect cases at the earliest possible moment was, next to strict aseptic and antiseptic routine in the labour and post-natal wards, the most important safeguard in hospital midwifery.

In regard to toxæmia, Dr. Fairfield's figures were not so encouraging. He was convinced that this constituted one of the greatest responsibilities for the hospital services of the future. The minor manifestations of the disease (hypertension, œdema, headache, &c.), should in a greater degree than at present be regarded as a

reason for hospitalization and more beds were necessary for this purpose than was generally recognized. In this connexion he quoted three cases showing how even what were usually regarded as minor manifestations of toxæmia, hypertension (140 mm. Hg.), œdema, and headaches, which quickly responded to rest, might presage danger. Two such cases admitted to hospital and discharged after subsidence of the signs and symptoms were readmitted after a short interval with concealed accidental bleeding, whilst a third was admitted with eclampsia. Such experiences were tending to convince him that unless adequate provision was made in maternity hospitals for the admission of cases of toxæmia, even in the earliest phases, it would be impossible to deal successfully with this second most important factor in the production of maternal mortality.

Dr. W. H. F. Oxley said that as one who knew the midwifery wards of the hospitals before they were taken over by the L.C.C., he was surprised and pleased to hear of the extraordinary service which had been created in so few years. It was gratifying to find that the mortality in booked cases was only 1·7 per 1,000. Dr. Fairfield's survey was the most exhaustive analysis in modern times and afforded some useful clinical results.

He would like to stress the value of immediate bacteriological examination in puerperal pyrexia, not only in the diagnosis but in the help it gave in searching for the origin of the infection. Although thorough isolation was necessary in streptococcal cases, he was inclined to believe that careful disinfection was sufficient to prevent the spread in cases caused by other organisms. The fact that only one death had occurred from sporadic infection following normal labour showed that the "police work" by the ward sisters had been very good.

It was worthy of notice that, although 90% of the L.C.C. patients received ante-natal care, there were still a good number of cases of eclampsia. He was not surprised at that, for in spite of the increase in ante-natal care in the country in the last ten years, the number of deaths from eclampsia had risen by 12%. The attempt to reduce eclampsia by examination of the urine had failed, and he thought that the prevailing ideas on the subject needed reconsideration. A considerable number of cases of orthostatic albuminuria (which occurred in 5% of normal males) were perhaps wrongly diagnosed in women as toxæmic.

Adherent placenta was, in his opinion, not so rare as Professor Munro Kerr had stated. It was not at all unusual to find a partially adherent placenta which had to be scraped from the uterine wall, leaving the latter furrowed like a ploughed field. He advised full chloroform anæsthesia during manual removal, in order to avoid shock.

The deaths from shock due primarily to the wrongful application of forceps comprised only a small proportion of the whole—he believed something like 5%—and it was expected that under arrangements which he hoped would be made in connexion with the Midwives Act 1936, they would be much reduced and would finally disappear.

The facts about rupture of the uterus brought out in the paper were interesting. This accident appears to have been of more common occurrence than one would expect in cases in which there had been no faulty midwifery. Perhaps the majority of the textbooks did not lay sufficient stress upon spontaneous rupture in elderly multiparæ.

Finally, the paper appeared to show that the securing of spontaneous labour (the interference rate being only 6%) and eternal vigilance in small everyday matters had more influence in lowering the death-rate than occasional brilliant work.

Mr. Arnold Walker: Dr. Fairfield has been able to draw upon a very large number of cases from London as a whole, and the only reason I can claim for taking up time is to present a small series from a restricted area which borders on the County

of London. I refer to the Borough of Willesden, with approximately 2,900 births a year. One-third of these deliveries takes place in the Willesden Maternity Hospital, and in 1936 no less than 60% took place in this or other institutions.

I have taken the booked deliveries up to the last few weeks. As this does not complete any particular period or number of cases, the rates I may quote will differ from those which appear in published reports and, as they have not been cross-checked, are given as approximate figures.

As Willesden is undergoing rapid industrial development and has a rising population, I thought it would be interesting to see what proportion of the mothers were actually born in and around London and what proportion could be described as immigrants coming into a prosperous area in search of work. I have, therefore, had recorded the birthplace of the last 1,000 or more women admitted to the hospital. The record shows that exactly two-thirds were born in London or the home counties, 9% came from the industrial North of England, 9% from the rest of England, 7% from Wales, 6% from Ireland, and only 2% from Scotland. Roughly speaking, in 4,500 cases, probably about 700 were born and spent their early life in the industrial areas of the North of England, Wales, and Scotland. As far as I can see, these immigrants have made little or no difference to the statistics, and contracted pelvis is as uncommon in Willesden as it is in those parts of London such as Poplar and Lambeth where the population tends to be essentially native.

The frequency with which disproportion is diagnosed depends very much on the observer, and it seems to me that the only way of comparing one series of cases with another is to take the number of cases in which Cæsarean section or induction of labour was performed on account of disproportion and to add to them the natural deliveries which ended in stillbirth or infant death due to intracranial trauma. This was worked out for the discussion here last year for a series of 3,000.

In the present series of about 4,400 booked cases Cæsarean section has been performed 15 times, before or during labour, feared mechanical difficulty, and in five other cases in which Cæsarean section had been performed elsewhere for various causes. Labour has not been induced on account of disproportion on any occasion. There were no cases of rachitic flat pelvis. No case required craniotomy on account of disproportion, except four in which there was hydrocephalus. The forceps rate for the series is about 4%, with a combined stillbirth and infant death-rate of under 12%. The total stillbirth rate is just under 3% and the infant death-rate about 1·8%. Amongst the booked cases, there have been five maternal deaths. The morbidity rate is under 5%, and in only two cases was a hæmolytic streptococcus identified. There was one death from anaerobic streptococcal septicæmia which followed an ante-partum *B. welchii* infection. Albuminuria occurred in 4·2% of cases, and in five cases out of the 174 eclampsia developed. All recovered, and their subsequent history is now under investigation.

The classification of breech deliveries varies from that of the unified system in that uncomplicated breech deliveries include primiparæ and multiparæ, extended limbs and flexed limbs. Complicated breech deliveries only include those with independent complications such as prolapsed cord, placenta prævia, or hydrocephalus. There have been 83 uncomplicated breech deliveries, of which 56 were in primiparæ and 27 in multiparæ. In these 83 cases there was one fresh stillbirth, one macerated fœtus, and four infant deaths of which two weighed about 3 lb. The stillbirth rate is lower than it is for vertex presentations. In the 56 primiparæ there was the one fresh stillbirth and two infant deaths, one of the infants weighing 2 lb. 13 oz. In at least 43 of the 56 primiparæ the legs were extended.

Miss Margaret Basden said that it was an honour to be associated with this great organization, and the consultants had opportunities of seeing in L.C.C. hospitals types of cases seldom met with elsewhere.

As an illustration she reported two cases and showed specimens from the first. One was in a woman admitted to hospital, not in labour, and showing symptoms of internal hæmorrhage. The diagnosis was complicated by a large cervical fibroid making it impossible for the head of the fœtus to enter the pelvis. On laparotomy, no cause could be found for the bleeding except a small tear in the spleen (which was removed), and a subsequent post-mortem examination by Sir Bernard Spilsbury revealed no other cause. (Subsequent examination of the spleen, however, by Dr. Barnard, failed to confirm a rupture.) The patient had improved temporarily with morphia and heat but was moribund at the time of the operation.

The other case was that of a woman admitted at the 36th week of pregnancy with symptoms suggesting a concealed accidental hæmorrhage, and from whose chest a large quantity of what appeared to be pure blood was aspirated. Post-mortem examination revealed a strangulated diaphragmatic hernia of the small intestine.

Mr. Eardley Holland said Dr. Fairfield had made it clear that the L.C.C. hospital administration was a system, whereas the voluntary hospital " system " was a collection of independent units between which any collaboration or co-operation was conspicuously absent. It was a great advantage to be able to collect and correlate figures and follow a standardized technique.

During the last two or three years it had become in many ways much safer for a woman to be confined in a first-class obstetric hospital than at home. But the hospital or department must be perfectly organized and equipped, and it should be sufficiently large to employ an adequate number of resident obstetricians and assistants, including one of really first-class experience and prestige, and whose salary should be attractive. The hæmolytic streptococcus was now under better control and the stage was being approached when the major problem of puerperal sepsis could be solved. Intrinsic infection by anaerobic organisms was as far off solution as ever. A great disadvantage of hospital confinements was that many women were scared by the ritual of preparations, and this might lead to uterine inertia of emotional origin. Everything possible should be done to counteract that.

The President said that he wondered if Dr. Fairfield fully realized the very great value, to those concerned for safe childbirth, of this survey, which must have involved much hard work.

The results tabulated were remarkably good and reflected great credit on those responsible for the care of these women. The recent fall in the death-rate from sepsis was especially important and was, no doubt, due to the conscientious use of full surgical aseptic and antiseptic precautions, during and after labour. Advantage should be taken of this. To give one instance : such precautions greatly lessened the danger of infection in manual removal of the placenta, and it was his strong opinion that the deaths which Dr. Fairfield had deplored might have been prevented by prompt manual removal of the placenta in cases of third-stage bleeding when expression had failed. In hospital practice, with plenty of assistance at hand, this dangerous operation could be carried out ever so much more quickly and safely than in a private house, and long before the patient was depressed by excessive blood-loss. Dr. Fairfield's figures would particularly interest those authorities who advocated institutional confinements.

During the last five years in at least five well-known hospitals in which face-masks and other precautions against infection by hæmolytic streptococci had been systematically employed under full bacteriological control, there was a lower rate of streptococcal infection amongst those delivered in the hospital itself than amongst the district cases.

Miss Basden's report of two rare cases was a reminder that there would always remain an irreducible minimum in the mortality rate.

Dr. Fairfield (in reply) apologized for having had to leave out a good deal of material, owing to lack of time, an omission which might account for some of the points which had been raised.

She had been glad to have encouragement in her contention that it was possible to keep the forceps rate too low. One of the things that her colleagues and herself had tried to keep in mind was never to work to percentages and figures. If one thought of percentages rather than of one's patient, was not that the beginning of bad work ? Each case must be taken and dealt with on its merits, and the welfare of both mother and child considered.

She quite agreed that the staffing and administration of the municipal hospital service needed to be a good deal further developed.

With regard to the kind of resident officers, every attempt was made to have in the unit someone with the M.C.O.G. diploma or, as a second string, someone who was working for it or for some higher obstetric degree. In midwifery, great importance attached to " the man on the spot ". There were always some cases which slipped through the net and gave bad results if there was a poor resident staff. Efforts were made to pool experiences ; units liked to feel that they were helping each other, and from time to time conferences were held at which difficulties were discussed, and an attempt was made to arrive at better methods and repair mistakes.

With regard to Cæsarean section, she was glad to hear the President's opinion of the improvement which could be shown in the Cæsarean section rate. There, again, one must not work to a rate, but must be prepared to consider each case with an open mind.

She expressed her gratitude for the kind way in which her paper had been received ; what had been said would, she was sure, be a great encouragement to the L.C.C. staffs, who were still working, and working well, under great difficulties.

[*March* 18, 1938]

The Problem of Post-Maturity

By F. Neon Reynolds, F.R.C.S.Ed.

Post-maturity has peculiar difficulties as a subject for discussion, since we have, at present, no definition of what we mean. It has a special interest for the practising obstetrician, and is a matter upon which there appears to be a great diversity of opinion. It is a question, too, upon which the patient cften tries to bring pressure to bear upon her medical attendant. If a woman is ten days or so beyond the reckoned dates, she herself, or her relations, very soon bring up the question as to whether something should be done.

As regards definition, we have one, I am told, of the opposite condition, i.e. prematurity. I understand that this Section and the B.C.O.G. have agreed that, in conformity with the standard in international use, an immature or prematurely born infant shall be taken, for the purpose of comparison of records, as one whose birth-weight is 5½ lb. or less, regardless of the supposed period of gestation. Although that seems to me to be rather begging the question so far as prematurity is concerned, it does give one something to work upon. With post-maturity we are in a worse plight, in that we cannot take weight as a guide, active treatment may be involved, and each individual has his or her own ideas as to what constitutes this state.

In this connexion, I attempted to obtain from hospital reports some idea of what is considered post-mature in the different hospitals throughout the country. In hospitals outside London I found 10 cases labelled as post-mature at anything from

40 to 42 weeks, and only one at more than 42 weeks. This was among 6,114 deliveries. In 4,815 deliveries in London hospitals there were 38 cases labelled as post-mature, of which 27 were 42 weeks or under. I think this might be considered a somewhat free application of the term if surgical interference is a necessary sequel.

There is no reliable sign, or collection of signs, by which an ante-natal diagnosis can be definitely confirmed or refuted, except perhaps in extreme cases. Fœtal development, well above the average as regards size, weight, ossification, &c., is not necessarily a result of prolonged gestation, just as immaturity is not synonymous with prematurity.

A search through the literature (Gould and Pyle, 1898, &c.) shows that the subject has been a matter of interest for many hundreds of years, but mainly from the legal point of view. In this respect it is interesting to note that the civil law of England gives no limit to the possible duration of pregnancy in determining questions of legitimacy. Most other countries allow about 300 days. Up to the beginning of this century the medical records are chiefly composed of a citation of cases said to be of long gestation, and resulting in legal proceedings, but showing little evidence of any scientific investigation. Even in recent years the available literature is very scanty, and of a somewhat unconvincing nature.

I am tempted to ask : " Does true post-maturity—that is, prolonged gestation—occur quite commonly, or only as an occasional freak happening ? " Whatever the answer, the subject is of practical importance, and worthy of discussion. I should like to consider it to-night from the point of view of ante-natal diagnosis and treatment.

Ante-natal diagnosis.—The usual method of determining the approximate date upon which labour should occur, is to take the first day of the last menstrual period, add on seven days (some people add ten days), and go back three calendar months. By this reckoning, we arrive at a date approximately 280 days from the beginning of the last menstrual period. This method is reasonably reliable ; a very large percentage of labours commence within a week or ten days of the date so calculated. This justifies us in concluding that the average period of gestation is between, say, 275 and 285 days. It does not necessarily mean, however, that a gestation lasting only 265 days, or apparently prolonged for 290 days, is abnormal. Such variation may be quite normal for the individual mother or fœtus, even though it does not conform to the average. In veterinary practice, where it is so much easier to ascertain almost every detail concerning the time of impregnation, it is found impossible to forecast parturition with complete accuracy. It is quite common for infants to be born fourteen days early, or late, without being in the least abnormal, compared with the standards we take as average, though I think this applies more to those that are late ; very often there are signs of prematurity in those born fourteen days early.

Other methods are of little use, and are much less reliable ; the date of quickening varies enormously in different individuals, or, at all events, the time of its detection varies. In all probability it does not, I think, occur at any definite period of gestation within several weeks. The size of the uterus is a still less reliable guide.

Whichever method of calculation one chooses, there is bound to be a large margin of error. Gestation is the period which elapses between impregnation of the ovum and birth of the child. It is very rarely possible to determine the exact day upon which the coitus responsible for pregnancy took place. Generally, we can only say that it was during the twenty-one days following the termination of the last menstrual period, and impregnation may have resulted from any one of these acts. We do not even know how long before a period is due it is necessary for impregnation to occur in order for that period to be suppressed ; it may be that this interval is as little as two days ; if so, in a case of this sort, the pregnancy would presumably continue for twenty-six days beyond term, in order to reach a full maturity of 280 days. I have recently seen a patient whose last period occurred on October 11, the next being due

on November 10. Her tubes were insufflated on October 28, and said to be blocked, so on November 4 lipiodol was inserted for X-ray investigation, which showed both tubes patent. Coitus took place on November 5 and 9. No further period supervened. It will be interesting to see when that baby arrives.

Even with detailed information regarding intercourse, we cannot determine the interval between coitus and impregnation, which again may be a variable factor. It is known that spermatozoa may live in the vagina for some days; they have been found in the tubes twenty-one days after coitus, but how long they can survive and still be capable of fertilizing the ovum is doubtful. The site of impregnation, though thought to be the fallopian tube, is uncertain, and this, again, may vary in different individuals. We do not, at present, know at what time during the menstrual cycle ovulation takes place. A considerable amount of investigation has been going on recently into this question (Hartmann, C., and others, 1936), but no definite conclusions have yet been arrived at. It is generally supposed that ovulation occurs somewhere about fourteen days after the onset of menstruation. If this is correct, and is constant, it would appear that conception must usually occur during the second half of the cycle, or that it must be possible for the ovum to survive in tube or uterus, for a very considerable period of time. Experimental evidence is, however, against this possibility. In the ideal case for determining the actual period of gestation, in which a single act of coitus is known to be responsible, there still remain these various unknown factors, which may upset one's calculation. In the few cases of my own, which come into this category, the length of pregnancy has varied only from 280 to 283 days from impregnation, and in each case it so happens that the coitus responsible occurred on the seventeenth or eighteenth day of the cycle, labour commencing seventeen to twenty days late by the usual reckoning. In those with a menstrual cycle of less than twenty-eight days the possibilities are narrowed down accordingly, and proportionately increased in those having a cycle of more than twenty-eight days. I have investigated this question, and find that the shorter the cycle the more accurate is one's forecast of the date when labour should occur.

What then are the factors upon which we can decide our standard of maturity, and will enable us to say that a certain individual has gone beyond full term? Various methods for investigation by means of X-rays have been worked out, with a view to solving this problem. There are those of Reece and McDonagh (1935) and Roberts (1935), which are based upon measurements of the fœtal head. It is difficult to believe that any diameter is such a fixed factor that it is possible to say, because this diameter is 3·75 in., that, therefore, the fœtus is of 40 weeks' maturity. There has certainly been great variation in the measurements that I have taken in newborn infants. Scammon (1937) in America, has even produced a most elaborate formula for measuring the crown-heel, or crown-buttock, length of the fœtus, from which he calculates maturity. It appears to me a little difficult to take these methods seriously, to the extent of determining by them when treatment should be instituted. Equally uncertain is the information given by an X-ray study of various ossification centres; the date of their appearance is not constant to within a week or so, and their identification presents various difficulties, depending as it does, upon such factors as the position of the fœtus *in utero*. More hope appeared to be held out some ten years ago, by investigations into the hormonal content of the mother's blood. The so-called placental reaction of the maternal blood (H. Sellheim, 1928) was said to show definite variations towards the end of pregnancy, and to reach a constant when full maturity was attained. If this should prove correct, it may eventually be possible to have tests made at intervals of a few days, and to get from them a correct indication of when labour should commence. One further test of a somewhat negative nature, should perhaps be mentioned. It is a fairly common treatment to give repeated small doses of some pituitary preparation, in an effort to induce labour. If this fails, particularly when it follows sensitization by castor oil and quinine, it is taken to

indicate that maturity is not complete, or, at all events, that the uterus is not ready for labour—a fairly safe conclusion.

Apart from these somewhat unsatisfactory aids, we are left, then, with nothing more than the information given us by the patient, upon which to reckon our dates. I do not think we can produce a basic standard in the present state of our knowledge, but is it necessary to have such a standard ? In other words, is treatment required simply and solely because a pregnancy appears to have continued beyond what we regard as its average duration ? If so, where do we draw the line, and say, " this fœtus is post-mature ? "

Now to come to the question of treatment : upon what evidence can it be said that treatment is necessary ? It is always held that a post-mature fœtus is in danger of intra-uterine death from placental degeneration. This statement is generally amplified by some reference to the added danger of a difficult labour from too big, or too hard, a head. If the head becomes too large, this at once removes the case from the category of post-mature, so far as treatment is concerned, and I believe that the head which is too hard, but not too large, is rather an anachronism, but I would emphasize the qualification contained in that statement.

What then do we mean by the term " placental degeneration ", and what evidence have we of its occurrence in connexion with post-maturity ? In the normal placenta, some degree of degeneration can be demonstrated, affecting the nuclei of the syncytium. It may be correct to say that this is more marked at term than in the earlier months. In other conditions in which we use this term, such as syphilis, the toxæmias of pregnancy, &c., a marked extension of this degeneration can be demonstrated in various different ways. A placenta from such a case can be shown to be affected in its vascular system, by means of injection and X-rays ; the changes are particularly well marked, as a rule, in cases of fœtal death ; microscopically, they can be confirmed, and they are generally evident, even macroscopically. Where the fœtus survives, there is often little alteration in the vascular tree. I have been unable to find, by any of these methods, either in my own very minor investigations, or in the literature upon the subject, any evidence at all of vascular or histological changes particularly associated with the post-mature placenta, and causing fœtal death. I think it is reasonable to say that intra-uterine death from placental degeneration has been more commonly applied to those cases in which death of the fœtus takes place a few weeks before term, in a patient who is not suffering from any of the toxic conditions mentioned. Such cases are well known, but rare, and I have not been able, for the purpose of this discussion, to investigate any of this nature, though I believe that, were pathological changes demonstrable in them, they would be well known by now, and would have found a place in the classical works upon this subject. It is certain that pathological conditions of the placenta occur very frequently, and without apparent harm to the fœtus. One very often sees multiple infarcts, sometimes involving as much as one-third of the placental tissues. Calcification, too, is very common, both as scattered flakes or as seed-like bodies, throughout the whole placenta, and in the latter form frequently appearing upon the fœtal surface as well as upon the maternal. It is perfectly definite that changes such as these are not associated in any particular way with post-maturity.

In attempting to find out something about this question, I felt that it was reasonable to assume that any change sufficiently severe to cause fœtal death must produce some vascular change in the placenta. This certainly applies to all other conditions in which there are placental changes associated with fœtal death. I have therefore confined my investigation of specimens to injecting them with lipiodol or other such preparation, and taking X-ray photographs. It seems to me that this method gives one a far better measure of placental function than any examination by microscopical means. In order to get any idea of how much tissue is involved, serial sections of the whole placenta would have to be examined. I fully agree with Professor Browne

(1937) when he states that senility of the placenta may cause intra-uterine death, but this is doubtful, as the functional reserve of the placenta is very large. There can be no doubt about that when one considers the gross changes seen in the placenta, without ill-effect upon the fœtus. Even purely mechanical causes may destroy large

FIG. 1.—Skiagram of an average placenta at full term, after injection with lipiodol. The regularity of the vascular tree is complete, except in one portion on the right of the photograph, which shows an area of infarction.

FIG. 2.—Placenta from a case of severe albuminuria, with living child, at the ninth month. Numbers of the terminal capillary tufts are entirely destroyed, or considerably reduced in size. A sufficient number of cotyledons, however, remain normally vascularized, to ensure the nutrition of the fœtus.

FIG. 3.—Placenta from a still more severe case of albuminuria, with very extensive destruction, resulting in fœtal death.

FIG. 4.—An injected placenta, from a case twenty-four days beyond full term. Practically the whole of the placental tissue is active, with a very complete vascular system.

areas of placenta without fœtal death. Good examples of this are seen among the Chinese, who frequently adopt the method of needling the uterus through the abdominal wall in order to procure abortion or premature labour. This is sometimes successful, but cases are reported (Maxwell, J. P., 1937) in which one-third or more of

the placenta has been destroyed by the resulting hæmorrhage, without causing fœtal death. It is easy to quote many references, in all of which the statement is made that post-maturity causes fœtal death from placental degeneration. In not one of the many I have searched through is a single description given of the pathological changes so produced. In several very exhaustive studies of placental pathology (Fournier, R., 1932, and others) every known condition leading to degeneration is mentioned, but not once does one come across the question of maturity. One is led, therefore, to entertain a strong feeling that this idea of so-called degeneration is one which has been handed on through the ages, without any pathological foundation. It may be that some physiological failure in function takes place, which causes fœtal death, but which we are not able to demonstrate by laboratory methods. If this were so, it would be reasonable to conclude that the fœtus dies from lack of nutrition, which would of necessity be a gradual process. The appearance of the post-mature baby does not support such a view, and the causes of intra-uterine death must be sought elsewhere.

I cannot see, therefore, any reason for carrying out induction—far less Cæsarean section—for the reasons commonly given, simply and solely because a woman is, say, three weeks past the time of her calculated term. At the same time, I must own to a feeling of anxiety in the matter when one has to decide between inactivity and operative measures. An investigation of the treatment adopted in hospital practice disclosed a very interesting position. In just over 11,000 deliveries there were 49 inductions or Cæsarean sections carried out for post-maturity, but of this 49, no fewer than 37 were given a maturity of 42 weeks or less. This leaves 12 cases of more than 42 weeks, of which 10 occurred in one particular hospital. This same hospital accounts for no fewer than 35 of the total 49 cases, labelled post-mature. The inference would seem to be that this hospital represents a definite school of thought in this matter, which is not followed elsewhere.

So much for hospital practice. In a careful analysis of 680 private cases, 49 were over fourteen days late and, of these, 23 were apparently post-mature by twenty days or more. In going through these, I have discarded all in which there was any element of doubt, such as those with a history of hæmorrhage, which might or might not have been menstruation ; so that these 23 patients were all definitely post-mature, by the ordinary standards of reckoning. There was one intra-uterine death—a case full of difficult factors, which would prevent one from using it in support of any particular argument, one way or the other.

Now I want to put forward a suggestion, which is by no means new, supported primarily by these 49 cases ; that is, that the apparent term of gestation is closely linked with the individual menstrual cycle, which must be considered in calculating maturity. In none of these 49 cases was the menstrual periodicity less than twenty-eight days ; among the 23 cases, which were twenty days or more overdue, there are five which might be called extreme, that is twenty-five, twenty-eight, thirty-five, and twenty-five days late ; these patients had cycles of thirty-four to forty-two days ; one with a twenty-six-day cycle was twenty-four days late. All had normal, and in fact easy, confinements, and live babies. I would like to quote one in detail. The first pregnancy was twenty-three days over the allotted time, and Cæsarean section was performed. When the second pregnancy occurred, the patient was anxious to avoid another operation. I was able to discuss the Cæsarean section with the surgeon concerned, who expressed himself as rather dissatisfied with the actual indications which decided him to operate ; he was not quite happy about the fit of the fœtal head, and finally felt that operation was the best procedure. When, for the second time, this patient was three weeks overdue, the problem was intensified somewhat by the previous Cæsarean section ; however, it was decided to keep her under observation, and on the thirty-fifth day after apparent full term, she had a very easy confinement, resulting in a healthy 9-lb. baby. This patient has always had a menstrual cycle of about forty-two days.

Now if my suggestion is correct, that such patients are not necessarily post-mature, but merely become pregnant late in the menstrual cycle, it would follow that the shorter the cycle, the less marked would be the tendency to apparent prolongation of pregnancy. In 24 cases with a cycle of about twenty-one days, there is not one in which pregnancy continued for more than ten days beyond the calculated date of full term. The conclusion, therefore, is, I think, that a pregnancy can continue beyond so-called term for as many days as there are in the individual's menstrual cycle, before necessarily being post-mature. My figures, I appreciate, are very small, but I believe that if it were possible to obtain a series of cases sufficiently large to enable one to form definite conclusions, the result would be the same.

I feel very certain that if I had applied induction or Cæsarean section to my 23 cases, as well as to others which were seventeen or eighteen days late, my results would have been no better. if as good. Furthermore, if one could collect, say 100 such cases, treated upon conservative lines, they would show, I venture to think, far better results, compared with the same number treated by operation or induction, even if the difference lay only in a question of maternal *versus* fœtal mortality.

There must, however, be a limit, I suppose, and I should value the knowledge as to what limit others than myself work to, how they base their calculations, and upon what evidence they institute treatment.

I should like to express my thanks to Dr. Bertram Shires for his help with many X-ray photographs, of which two examples (figs. 1 and 4) are reproduced, and also to M. Fournier and the Editors of *Gynécologie et Obstétrique* for their kind permission to use figs. 2 and 3.

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Professor F. J. BROWNE said he had never met with a case of ante-partum death of the fœtus in which the death could be attributed to post-maturity. He agreed with the speaker that ossification, as shown by X-rays, did not provide any reliable evidence of post-maturity. An ossific centre might appear in the lower end of the femur in the eighth month and might not be present at term, while a centre in the cuboid was only valuable in that it showed that the pregnancy had reached the 36th week.

In diagnosis of post-maturity, scrutiny of the menstrual history was important. On careful inquiry it was often found that the patient had been in the habit of occasionally missing one or two periods, and it might therefore be assumed that a month or more of pathological amenorrhœa had immediately preceded the pregnancy. His own practice was to ignore apparent post-maturity unless the patient had gone a fortnight past her expected date of delivery. If the scrutiny of the menstrual history disclosed no doubtful circumstance, a medicinal induction was given as a test. If labour did not then come on she was assumed to be not post-mature. He did not think that any relation had ever been or could be established between post-maturity and the type of the menstrual cycle.

In his opinion the only danger of post-maturity was a difficult labour arising from undue size of the fœtus or advanced ossification of its cranial bones.

Lower Segment Cæsarean Section.—R. H. PARAMORE, F.R.C.S.

Mr. Paramore described, by means of a cinematograph film, a special technique for the lower-segment Cæsarean operation, and discussed certain methods of pre-medication, preparation for operation, and the choice of anæsthetic. Spinal anæsthesia was used in most cases.

The chief difference between this and the ordinary technique, was in the treatment of the peritoneum. In Mr. Paramore's operation the upper peritoneal flap of the uterus was sutured to the upper peritoneal flap of the abdominal wall, which was opened by transverse incision, and no attempt was made to reconstruct the utero-vesical pouch.

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Section of Orthopædics

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[*February* 1, 1938]

Fractures of the Metatarsals

By C. Gordon Irwin, F.R.C.S.

In the North of England we live amongst the heavy industries—the iron and steel trade, and shipbuilding, for example—and a very large population works in the coal mines. On making inquiries, I found that of 3,400 accidents in the iron and steel works, 380 involved fractures of the bones of the foot; 35 of these were fractures of the metatarsals, in the year 1936. This figure was supplied by one insurance company which practically deals with only one trade. In the first six months of 1937 we had 68 cases of fractures of the metatarsal bones in the Clinic at Newcastle.

Those of us who spend much of our time dealing with bone injuries almost unavoidably become involved in the compensation issue, and one's pessimism as regards results may have been due to this fact, but after the dissection of a large number of recent results one is much happier than hitherto, when the analysis of hard facts and figures in the past has always acted as an efficient damper to surgical optimism.

Ten years ago it was a more serious matter to sustain one of these fractures than it is to-day; I am grateful to insurance companies for this information. Compensation was paid on a total or partial rate in respect of such injuries, substantiated by X-ray examination, in 50 individual consecutive cases for an average period of eighteen weeks. In 1936 the Iron Trades Insurance Company averaged payment in cases of metatarsal fracture for eight and a half weeks, whilst an analysis of 54 consecutive cases dealt with from all forms of accidents and trades in the Fracture Clinic, from the date of injury to the time of return to full work, shows the figure to be twelve weeks. These figures are taken from the period of January to June 1937. Possibly some of this improvement is due to the segregation of the fractures and the standardization of treatment with reasonable follow-up facilities. The subject is one of almost national importance, both from a humanitarian and an economic standpoint.

As we are primarily dealing with treatment I do not propose to go into details of the physiology of function and the anatomy of the foot, although naturally any such treatment would aim at as complete a restoration as possible. The more I have studied the problem, and the more clinical material I see, the more "Mortonized" do I become, as it is increasingly apparent that ligament and bone shape are more valuable stabilizers of form than mere muscle action is, and that if the size, shape, or mobility, of that principal prop, the 1st metatarsal, is abnormal, the foot is liable to many pathological changes and to the development of severe functional disabilities. An early appreciation of that fact obviates many late complications after trauma.

The metatarsals are fractured by either direct or indirect trauma, the commonest form of injury being the dropping of some article on to the dorsum of the foot, or the squashing of the foot by the wheel of a vehicle. The indirect variety, which largely concerns the base of the 5th, is caused by a twist of the ankle, the type of trauma that so frequently involves the fibres of the external lateral ligament of the ankle, with avulsion of the attachment of the peroneus brevis at the base of the bone; or the toe

of the shoe may be caught in a grating, and the patient in falling forwards may crack through the 2nd or 3rd metatarsals at their necks.

Of 50 accidents 34 were associated with direct, and 16 with indirect, violence. The prognosis of the case can only be assessed after the type of accident has been reviewed, the direct type inflicting a varying degree of injury to the soft tissues, both on the dorsum and in the sole of the foot. It is this factor that usually produces interference with foot function.

The reduction of deformity.—In by far the greater number of cases no reduction is necessary as the alignment is maintained. On the other hand, many of these cases are difficult to diagnose from a skiagram, some even requiring an enlarging glass to confirm suspicion.

Failure to diagnose even a small crack in a metatarsal may be responsible for several months' difficult walking. The crack may be almost indiscernible on the day of the injury, but as weight-bearing on the fore part of the foot persists, the fragments rock and bend into a mild deformity, with the production of a great deal of new bone, which may involve the soft structures of the sole and cause pain and œdema. If there is any reasonable ground to suspect a fracture, the injury should be treated as one.

When the middle metatarsals are fractured obliquely, and the 1st and 5th remain intact, there is rarely much deformity, and such as it is can usually be corrected manually, and the reduction easily maintained.

If the 1st metatarsal is fractured great care must be taken (1) to correct any impaction, and (2) to be certain that any angulation shall not project towards the sole. Should either of these things happen, the subsequent weight distribution will be flung on to the 2nd or 3rd metatarsals, with serious complications to the transverse arch and the mid-tarsal region. If angulation is to occur it is better to have the angling towards the dorsum of the foot, and the head of the bone projected, if anything, into a more than usual prominence. Care in this respect leads to comfort and function.

In the severe direct-violence injuries all the bones may be fractured, usually slightly nearer their bases than their heads, with a gross amount of displacement in one or the other direction, depending on the application of the force that produced the lesion. In many of them the typical step-deformity is visible as well as palpable. The sooner this is reduced the better. Attempts at manual reduction in these cases are usually futile, and merely produce an increase of the damage to the soft parts which are already often œdematous and lacerated.

The method advocated and practised by Bohler offers the most certain and rational means of effecting anatomical restitution. There may be some doubt as to when such reduction should be attempted. If the parts are swollen and œdematous it is wiser to elevate the limb for twenty-four hours before operation, on a Braun's splint and with the end of the bed elevated.

Personally, I prefer general anæsthesia for the operation. Local injections are inclined to increase the swelling and make palpation more difficult. Moreover, I believe that most surgeons in this country prefer the moral comfort of an unconscious patient, as I do.

Wires are passed by a needle-holder through the tips of the toes. The ends of each wire are threaded through holes in small pieces of wood, and tied over a round stick. The ankle is retained in a fixed position by a pad of webbing, and is firmly held either by an assistant or by means of a hook in the wall. The webbing is spread by means of a piece of board. Traction is then made on the rod through the individual toes; this may have to be kept up for some time. The reduction of the deformity will be obvious. Portable X-ray apparatus is of great assistance.

With the traction still maintained, the plaster cast is applied, carefully moulded to the arch of the foot, and if there is any tendency for displacement to recur an

extension is added to the plaster and the wires tied to it. The foot is then put up on a Braun's frame, and the extension is retained, if necessary, for a week. As the swelling subsides it is replastered, and the deformity does not recur.

In all cases of fractures of the metatarsal bones plaster of Paris seems to be the most efficient means of immobilization applied, after reduction, from below the heads of the metatarsals to just below the knee. During its application the foot is held at a right-angle, and while it is hardening it is moulded carefully to the supported arches of the foot, particular care being taken to include the head of the first, which should be depressed.

Half a "sorbo" rubber ball may be incorporated in the plaster at the heel. It is a cheap and efficient walking support, and diminishes the unpleasant jarring of a walking-iron or straight plaster.

If the case is a simple one, with only one or two fractures, and with little œdema, the patient is encouraged to walk forthwith and, if an out-patient, is required to report at hospital in four days. It may then be found that owing to decrease in the traumatic œdema the plaster is slack and requires renewal. Failure to carry out this precaution will lead to disappointing results, as it is imperative that the general conformation of the foot should be efficiently supported throughout the treatment. Walking with an efficient plaster, far from increasing swelling, tends to diminish it; the circulation is maintained, and the lymphatic efficiency is improved.

Of recent years the walking-plaster has become a complete vogue. Our profession has realized how effective a treatment it is, as, apart from increasing the morale and excursion of the victim, it produces the quickest result both in the healing of the bone and the maintenance of muscular and vascular tone.

The complete immobilization and control of fractured bone-ends, in anatomical alignment, is the first principle of good fracture treatment. In my opinion the encouragement of muscular stress in the normal plane is the second important factor. I believe that the activating stimulus to the efficient work of the osteoblast is stress; in other words, within certain limits we happen to be the shape we are, for better or worse, as a result of gravity and our muscle action. Woolfe, years ago, working on the neck of the infant femur, proved that this bone never became what we call a normal femur unless the child walked.

A fractured rib never, to my knowledge, fails to unite, because no matter how efficiently we strap the chest wall the intercostals continue to exert their muscular action. Those of us who after the Great War carried out large numbers of bone transplants were at times disappointed to find that after long periods of immobilization some of the long bones failed to unite. After removal of the fixing apparatus, and the instigation of what function the limb was capable, we were surprised, months later, to find union good and function improving.

After the adequate reduction of an overlapping femur, and the efficient maintenance of its correction, our patients are forthwith taught how to contract the individual groups of muscles in the thigh without actually moving a joint, thereby supplying the muscle stress to the fractured ends, as well as the prevention of the formation of adhesions to the fracture itself. The mere fact of walking in a walking plaster with a fracture of a metatarsal bone produces muscular contraction and the incentive to osteoblastic reaction, and early and efficient union results.

The plaster should be retained, even in simple crack fractures, for a month, and in more complicated ones from five to six weeks. After its removal the patient is fitted with a transverse metatarsal strap and pad, while the inner side of the sole and heel of the shoe are raised by a quarter of an inch. These supports are retained for three months. Should the patient have a congenital short 1st metatarsal, which is a common condition, and the fractures be in the 2nd, 3rd, or 4th, a quarter-inch pad is fitted into the shoe to support exactly the length of the 1st metatarsal, preventing increased mobility of this bone, and emphasizing its weight-bearing.

A survey of the results of 54 consecutive cases dealt with in this manner at the Fracture Clinic shows that the average period away from work on account of a fracture of the metatarsals by indirect violence is eight weeks and a half, and that on account of a fracture due to direct violence, thirteen weeks. None of the patients in this series were treated by massage.

Comparative frequency of the fracture of individual metatarsals :—
1st, 53 ; 2nd, 43 ; 3rd, 70 ; 4th, 58 ; 5th, 58.

RESULTS OF 54 CONSECUTIVE CASES TREATED AT THE FRACTURE CLINIC.

Royal Victoria Infirmary, Newcastle-upon-Tyne.

No.		Age	Meta-tarsal fractured	Direct (D.) or indirect (Ind.) injury	Weeks off work	Present condition
1	J. K.	22	3, 4	D.	16	No pain if wearing pad
2	R. T.	13	5	Ind.	6	No symptoms
3	C. W.	53	1	D.	13	No symptoms
4	A. D.	42	1 (C.)	D.	8	No pain, must wear pad of quarter inch
5	J. C.	60	3, 4	D.	12	No symptoms
6	W. K.	54	2, 4, 5	D.	24	Pain ; swells ; working as a miner
7	D. J.	18	3, 4	Ind.	7	No symptoms
8	J. S.	54	5	Ind.	8	Pain if wedge not worn
9	M. W.	39	5	Ind.	6	A little pain in bad weather
10	W. T.	58	4, 5	Ind.	8	No symptoms
11	R. M.	39	1	D.	16	Pain at end of day's work
12	M. S.	53	5, 1	Ind.	6	No symptoms
13	D. P.	49	5	Ind.	4	No symptoms
14	J. J.	43	3, 5	Ind.	12	No symptoms
15	L. T.	31	4, 5	D.	11	No symptoms
16	R. W.	52	1, 2	D.	14	Slight pain
17	M. G.	46	3	Ind.	9	No symptoms
18	W. S. M.	62	1	D.	11	No symptoms
19	S. G.	39	3, 4	D.	11	No symptoms
20	E. C.	18	1	D.	12	No symptoms
21	W. C.	47	5	Ind.	12	No symptoms
22	L. M.	15	1, 2, 3, 4	D.	12	No symptoms
23	T. C.	53	1, 2, 3, 4	D.	12	No symptoms
24	S. B.	40	4	Ind.	6	Slight pain in bad weather
25	M. S.	59	5	Ind.	7	Slight pain
26	J. P.	46	2, 3	D.	10	Slight pain in bad weather
27	R. S.	38	3, 4, 5 (C.)	D.	10	No symptoms
28	A. A.	20	1	D.	8	No symptoms
29	P. M.	21	1	D.	15	Some pain in stiff toe-joint
30	R. P.	15	1	D.	11	No symptoms
31	T. W.	45	4, 5	D.	20	No symptoms
32	C. T.	34	5	Ind.	4	No symptoms
33	W. C.	53	4, 5	D.	16	Some pain in bad weather
34	E. H.	55	3, 4	D.	8	No symptoms
35	G. W.	23	2, 3	D.	8	No symptoms
36	W. P.	35	2, 3, 4 (C.)	D.	12	No symptoms
37	A. L.	49	3, 4 (C.)	Ind.	24	No symptoms
38	E. C.	38	1 (C.)	D.	20	Still on light work owing to some swelling
39	T. T.	50	1, 2, 3	D.	12	No pain if wearing pad
40	D. C.	61	2, 3, 4	D.	15	Slight pain in bad weather. Full work
41	J. W.	31	3, 4, 5	D.	8	No symptoms
42	J. L.	22	1, 2, 3	D.	10	No symptoms
43	J. R.	48	1, 2, 3	D.	16	No symptoms
44	H. T.	36	5	Ind.	7	No symptoms
45	T. M.	28	3	D.	15	No symptoms
46	J. H.	26	2	D.	12	Slight pain, but works full time
47	R. J.	59	3, 4	D.	11	No symptoms
48	J. H.	33	5	Ind.	8	Slight pain in bad weather
49	I. D.	25	1, 2, 3, 4, and 5 (C.)	D.	28	Full work as miner
50	W. E.	53	2, 3	D.	10	No symptoms
51	R. I.	34	5	D.	12	No symptoms
52	A. M.	50	2, 3	D.	10	Tired feeling at end of day's work
53	W. N.	34	1, 2, 3	D.	12	Some stiffness in big toe ; working
54	G. S.	45	1, 2, 3	D.	16	Working as miner. Stiffness at ankle by night

I may here say a word about march fracture. A delightful explanation of its ætiology was given by Murk Jansen in a paper read at a meeting of the British Orthopædic Association at Manchester in 1925, in which the author said : " A march foot is to the mid-foot what spastic flat-foot is to the lower leg." He ascribes this spastic change to a spasm of the interossei which prevents the flow of blood and lymph through their structure, thus giving rise to a local œdema. This œdema spreads to the periosteum, and by its pressure causes an absorption of lime salts and an imperceptible fracture.

I have found a reference stating, so recently as 1932, that a very " competent surgeon " recommended amputation for a march fracture, diagnosing the condition as a sarcoma. Fortunately the metatarsal was excised and examined microscopically as a preliminary. The section showed well-formed new bone with local hæmorrhage and a uniting fracture.

In the Army during the Great War it was a well-recognized condition, and the relative frequency of its occurrence gave some index to the fitness of marching troops. In civil life, however, it still persists, and I have seen three cases in nurses during the last six months occurring in the early months of training. The condition appears to manifest itself in an over-strained foot unaccustomed to prolonged periods of standing. It not infrequently occurs in people who have a congenital short 1st metatarsal, or a hypermobile one, in which the weight-bearing stress is thrown directly on to the thinner and more fragile units. These cases rarely come for treatment until the fracture has taken place. It is then wise to immobilize the foot until consolidation has been effected, and when work is to be resumed the patient should undergo a course of training. Particular emphasis should be laid on the importance of adequate support for the 1st metatarsal, otherwise if the patients begin work again without any effort having been made to prevent a recurrence, a second fracture may manifest itself, and a further period of immobilization and treatment may be required.

Fractures of the Phalanges of the Hand and Metacarpals

By Norman Roberts, F.R.C.S.

The figures in this paper are based on a series of 1,200 fractures of the phalanges and metacarpals, the reports of which I have collected from the records of the Fracture Clinic at the Liverpool Royal Infirmary.

It is clear from the number of cases that these injuries are very common, and the frequency with which malunion and stiffness of the fingers are seen indicates the importance of correct treatment. Loss of grip and of the usefulness of the hand is a more serious disability than the worst results of an incorrectly treated elbow or shoulder injury, and I feel that there is too great a tendency to regard these injuries of the hand as minor and trivial accidents, which are not worthy of the attention of the visiting surgeon and can safely be left in the hands of an inexperienced house surgeon.

Fractures of the Phalanges of the Fingers

The total number of cases in this group was 510. Chip fractures and intra-articular fractures accounted for 73 cases. The shaft of the proximal phalanx was fractured in 286 cases, the intermediate phalanx in 51 cases, and the terminal phalanx in 100 cases.

(1) *Fractures of the terminal phalanx.*—The majority of these injuries are crush fractures, involving the tip of the phalanx, and are often complicated by injuries of the soft tissues and nail. Recovery in these cases depends largely on the progress of the soft tissue injury and the fracture itself does not require treatment in the ordinary case. Immobilization for a short period may be necessary if there is much swelling,

or any infection, but every effort should be made to encourage active movements of the finger as soon as possible. Chip fractures of the base of the phalanx are seen following direct injury, and a chip fracture of the dorsal surface of the base is seen in mallet finger. Transverse fractures of the body of the terminal phalanx may be slow in uniting, and if non-union supervenes and there is any impairment of function disarticulation through the terminal interphalangeal joint may be necessary.

(2) *Fractures of the intermediate phalanx.*—Fractures of this phalanx are relatively uncommon and there were only 51 cases (10% of all fractures of the phalanges). The fracture is through the middle of the shaft and the common deformity is one of forward angulation. The treatment does not differ essentially from fractures of the proximal phalanx and need not be considered separately.

(3) *Fractures of the proximal phalanx.*—There were 286 fractures of this phalanx, accounting for more than half of all the phalangeal fractures. The typical fracture is a transverse one in some portion of the proximal half of the phalanx, usually about the middle of the shaft. Forward angulation occurs, often complicated by lateral displacement and angulation, together with a rotation deformity. One commonly sees these fractures treated with the finger in extension, and in this position it is very difficult to secure correction of the deformity. The fracture unites with some degree of forward angulation which seriously hampers the action of the flexor tendon, and when finger movements return it is found that there is a rotation deformity so that the fingers become crossed in the position of full flexion. This rotation deformity is very difficult to detect when the finger is in the extended position.

Various methods of splintage of the finger in the flexed position have been devised, many of them employing continuous traction to maintain the reduced position. It is doubtful whether this is necessary, except in comminuted fractures with a tendency to shortening. If a simple transverse fracture has been well reduced and splinted in the flexed position without traction there is no tendency to recurrence of the deformity or shortening. A palmar splint of bent wire or plaster is made to hold the finger in the flexed position and reduction is secured by traction with the knuckle-joint flexed. The fingers should lie parallel in the flexed position, to obviate any rotation deformity. A simple method of splinting, which I usually employ, is to strap the finger down in the flexed position over a tight roll of wool or bandage placed in the palm. If only one finger is involved, care should be taken to see that the roll in the palm does not lie across the whole breadth of the palm and thus prevent free movement of the uninjured fingers. The strapping is applied along the dorsum of the hand in the line of the metacarpal and along the whole dorsal surface of the finger to the front of the wrist, where it is secured by an encircling band of strapping. It is often possible to dispense with the roll in the palm, in order to give complete freedom of movement for the remaining fingers. The patient is instructed in active exercises of the uninjured fingers, and should be supervised carefully during the first week to see that these exercises are carried out.

The finger is splinted for from two to six weeks, according to the severity of the fracture and the age of the patient. Movements are usually slow in returning, especially if the fracture has been close to the proximal interphalangeal joint. No attempt should be made in the early stages of recovery to assist movement and the patient should rely entirely on his own active endeavours. In cases of severe fracture with marked swelling, and in old people, extension movement at the proximal inter-phalangeal joint may be very slow in returning and some months may elapse before final recovery is reached. This troublesome stiffness appears to be an unavoidable complication of finger injuries, and the most that can be done to prevent it is to cut down the period of immobilization to as short a time as possible. Provided the patient avoids further injury to the finger and relies only on active exercises it is often possible to abandon rigid splintage of the finger after the first two or three weeks while the fracture is still tender and not firmly consolidated. Careful watch must be kept for any recurrence of the forward angulation deformity.

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PLATE I.

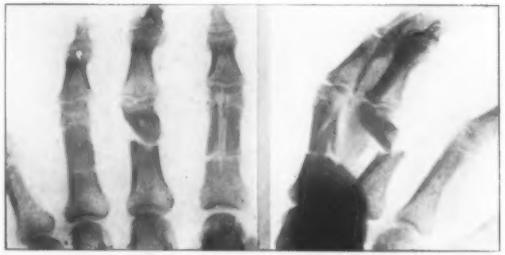

FIG. 2.—Typical fracture of the proximal phalanx with forward angulation deformity.

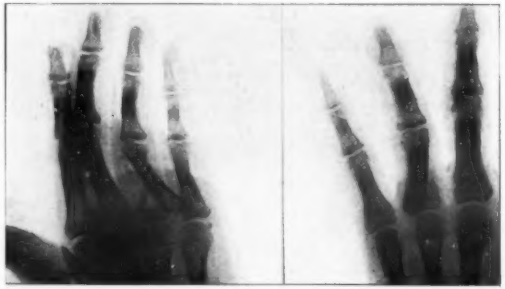

FIG. 3.—Malunited fracture of the base of the proximal phalanx following treatment on a straight splint.

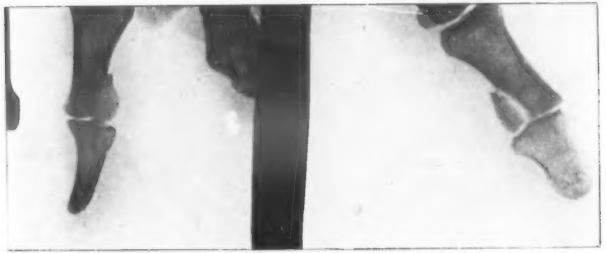

FIG. 4.—Condylar fracture involving the interphalangeal joint of the thumb.

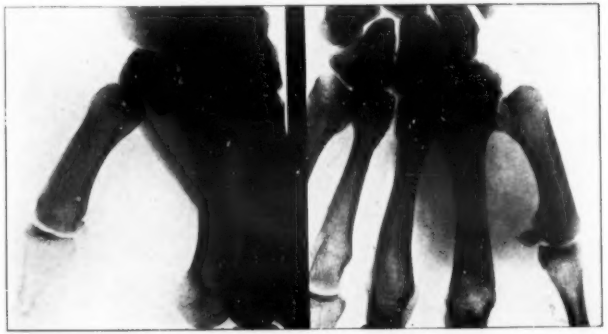

FIG. 5.—Typical Bennet's fracture.

PLATE II.

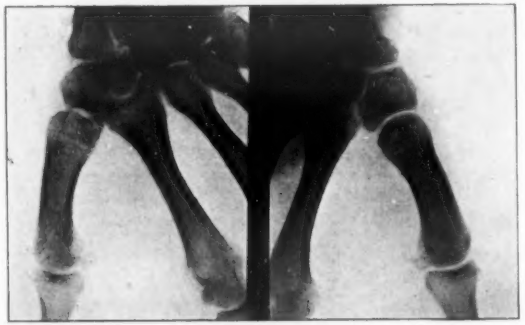

FIG. 6.—Same case as in fig. 5 six weeks later. Treated by continuous traction.

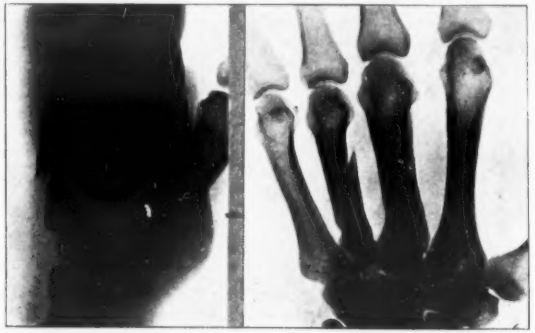

FIG. 8.—Spiral fractures of the shafts of the 3rd and 4th metacarpals. Despite the shortening no treatment by traction was employed in this case.

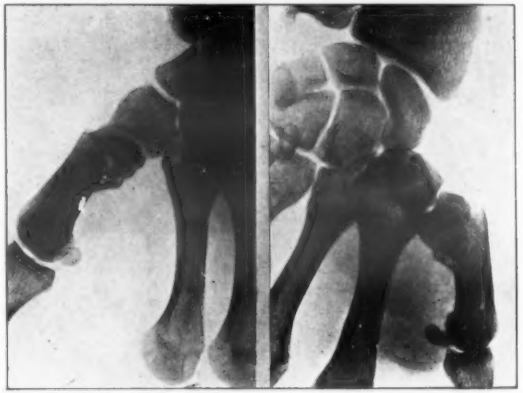

FIG. 7.—Fracture of the base of the 1st metacarpal with posterior angulation.

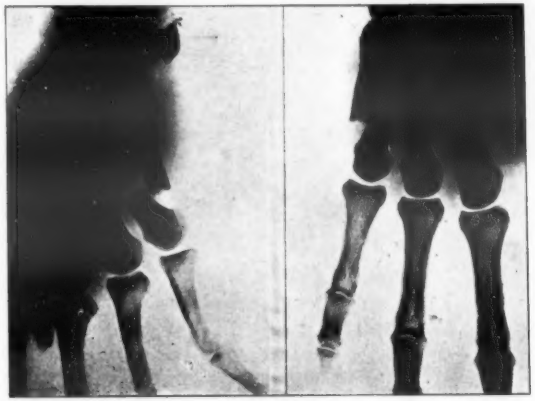

FIG. 9.—Transverse fracture of the shaft of the 5th metacarpal. Treatment by continuous traction is necessary in this type of case.

Fractures involving the interphalangeal joints.—There were 73 cases in this group. The majority were chip fractures of the marginal joint-surface complicating a sprain or dislocation of the finger. The fracture was commonly detected late, when an X-ray film was taken to account for the slowness in recovery of a sprain of the finger. There was a fusiform swelling of the affected interphalangeal joint and painful stiffness. The clinical appearance did not differ from that of similar chronic sprains of the finger without fracture, and it is doubtful whether the presence of such a chip fracture is of any importance. Operative removal, or replacement, of the detached fragment is probably misguided enthusiasm and is likely to increase the stiffness of the affected joint.

Other intra-articular fractures show varying degrees of displacement and deformity with or without a dislocation of the interphalangeal joint. In the presence of any deformity, treatment by fixation in the flexed position, if necessary with traction, will minimize the displacement, but the prognosis is bad and painful stiffness of the affected joint is very common. Operative re-position may improve the X-ray picture but, as in intra-articular fractures elsewhere, the results are disappointing. The cases should be treated by a short period of splintage followed by active exercises, and if movements of the affected joint show no signs of improving an early decision should be made as to whether amputation is advisable. Many of these patients attend hospital for massage and physiotherapy for long periods and eventually have the finger amputated many months after the injury. This prolonged disability period can be shortened considerably by an early amputation as soon as it becomes obvious that the finger will not recover. This applies particularly to those intra-articular fractures involving the proximal interphalangeal joint.

Fractures of the First Metacarpal

The total number of cases in this group was 185. Fractures of the base of the metacarpal accounted for 173 (93%) of these. Seventy-three belonged to the fracture-dislocation type with involvement of the carpo-metacarpal joint and the remaining fractures involved the base of the metacarpal without extension of the fracture line into the joint.

(1) *Bennet's fracture.*—This type of fracture was found in 73 cases. The average age was 36 years, and 91% of the patients were males. The primary injury is an outward subluxation of the base of the metacarpal and the secondary injury is a triangular or comminuted fracture of the "beak" which remains in its normal position as the base of the metacarpal displaces outwards. The subluxation can easily be detected on clinical examination and is comparatively easily and painlessly reduced by traction on the thumb and local pressure. If the traction is released the subluxation recurs. A position of extreme abduction and extension of the thumb is favourable to maintaining reduction. Most methods of splintage without traction are open to the objection that although the first reduction may secure a good position, relapse is likely to occur with recurrence of the subluxation. Malunion of these fractures results in a severe osteo-arthritis which is often a cause of disability in later years. The disability is seldom serious enough to prevent a patient from doing labouring work, but this fact does not justify carelessness in treatment.

Treatment by some form of traction in abduction and extension of the thumb is the most effective and certain method of maintaining reduction of the deformity. The most easily applicable method is to construct a wire frame in the manner of a Thomas splint and to incorporate this in a dorsal plaster case which fixes the wrist joint. Traction is then made on the thumb and local pressure is applied over the base of the metacarpal by means of a felt pad secured with strapping. The plaster should not cover the first metacarpal, so that the position can be checked by clinical examination from time to time. Continuous supervision of the traction and pressure pad is necessary, and with attention to detail it should be possible to secure perfection in all cases except those in which there is comminution of the base of the metacarpal. The period of fixation should be in the neighbourhood of six weeks.

(2) *Fractures of the base of the thumb metacarpal (not involving the joint).*—There were 100 cases in this group, 36 of which were juvenile injuries. Sixty-four occurred in adults at an average age of 27 ; 93% were in males. The characteristic deformity in these cases is similar to that of a Bennet's fracture, but the angular deformity is independent of any injury to the carpo-metacarpal joint, which is uninjured. The fracture is often untreated and unites with backward angulation, leaving a local prominence for which the patient seeks advice. The angular deformity limits abduction movement of the thumb a little but does not account for any painful symptoms and the function of the hand is unimpaired. In cases seen early, reduction of the fracture is accomplished by a forcible manipulation under anæsthesia. The fracture is frequently impacted and may be difficult to reduce. If it is not reduced by a forcible manipulation, simple traction in itself is not capable of correcting the altered axis of the metacarpal. The reduced position should be held by a dorsal plaster case incorporating the thumb as far as the interphalangeal joint. The thumb is incorporated in the plaster in abduction and extension and the plaster is moulded closely over the base of the metacarpal. Fixation should be for about four weeks, and with care it should be possible to secure full reduction of all cases. However, minor degrees of persistent displacement do not account for any disability and for this reason open reduction of delayed cases does not commend itself.

(3) *Other fractures of the first metacarpal.*—Apart from injuries to the base, fracture of this metacarpal is uncommon. There were six fractures of the neck and head of the metacarpal in this series and three fractures of the shaft. Three cases of fracture of the sesamoid on the ulnar side occurred as the result of hyper-extension injuries. There was no displacement and they recovered quickly.

Fractures of the Other Metacarpals

The total number of cases in this group was 516, of which 84% were in males, the average age being 28 years. The distribution of the fractures is seen in the illustration (fig. 1).

(1) *Fractures of the neck.*—Fracture of the neck of the 5th metacarpal is a very common injury. The invariable deformity is one of posterior angulation, with lateral deviation or angulation to one or other side. Correction of the deformity in recent cases is easily accomplished, but the fracture is often unstable and the deformity tends to recur. The corrected position is held by a dorsal plaster cast including the proximal phalanx of the affected finger. Traction is of no value in correcting the deformity and its use is unnecessary. Three or four weeks' splintage is necessary and the hand quickly returns to normal. If malunion occurs the function of the hand is not impaired, and no interference is advisable if more than a week or two has elapsed since the fracture.

Fractures of the neck of the other metacarpals are similar to those of the 5th, the index metacarpal being the next most commonly injured in this way.

(2) *Fractures of the shafts.*—The 4th and 5th metacarpals are most commonly involved in fractures of the shaft and the index metacarpal is least commonly affected. The fracture may be oblique, spiral, or transverse. The index and 5th metacarpals are especially liable to transverse fracture which in both of these bones is more common than a spiral fracture. This is probably owing to the fact that they are more exposed to direct injury which is the commonest cause of the transverse fracture. Fractures of the 3rd and 4th metacarpals are oblique or spiral in 75% of the cases. The deformity in such fractures is usually only slight and is in the direction of shortening without much angular deformity. Transverse fractures usually show some angular deformity and in the more severe cases there is complete loss of apposition, with angulation of the fragments backwards. The occasional cases of non-union are seen in transverse and low oblique fractures with displacement or following a compound injury.

Treatment of fractures of the shaft of the metacarpals need not be taken too

seriously. Errors in treatment are most commonly due to over-splintage, with resulting stiffness of the fingers. In the majority of cases it is unnecessary to attempt reduction of the slight shortening by traction, since in the presence of swelling of the dorsum of the hand and fingers traction may lead to serious stiffness of the affected finger, and a long period of disability. It must be remembered that in the ordinary case of fracture of a metacarpal the natural recovery proceeds quickly and functional disability of the hand is rarely seen. All that is necessary in the oblique and spiral fractures is the application of a dorsal plaster cast and the early institution of finger movements. Finger movements should be full within a day or two and the patient will be ready for work in about four weeks. If there is any angular deformity this is corrected by a manipulation, and recurrence of backward angulation is prevented by moulding the plaster closely over the dorsal surface of the injured metacarpal. The plaster may be prolonged to include the proximal phalanx of the injured finger.

The common practice of bandaging all the fingers of the hand over a roll of wool or bandage cannot be too strongly condemned. The method is often used in trivial

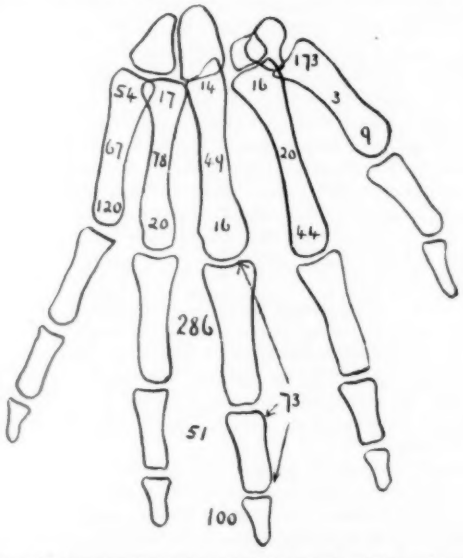

FIG. 1.—Sketch showing the comparative frequency of fractures of the metacarpals and phalanges.

cases without appreciable displacement, and in the presence of swelling of the fingers there is a great danger of serious and permanent stiffness of the fingers.

In the more difficult cases, particularly in transverse fractures which are very unstable and grossly displaced, simple fixation of the fracture is not sufficient and traction is necessary. Traction is applied by skin extensions or by a wire through the pulp of the finger, the knuckle being flexed at least 45°. Any method which involves traction or fixation with the knuckle-joints in the extended position is to be avoided. The most serious cases of stiffness of the fingers following injury to the hand are those in which the knuckle-joints are held rigidly in the extended position.

Fractures of the base of the metacarpals.—The base of the 5th metacarpal is most commonly affected. The fracture frequently involves the carpo-metacarpal joint and in some ways resembles a Bennet's fracture. Very occasionally a slight subluxation of the base of the metacarpal is seen in association with the fracture. The deformity is seldom marked. Similar fractures of the base occur in the other

metacarpals and occasionally the deformity is marked and necessitates a formal reduction and splintage with or without traction. The prognosis is good and the involvement of the carpo-metacarpal joints does not seem to lead to any appreciable symptoms.

The Role of Manipulation in the Treatment of Finger and Hand Injuries

Knowing that stiffness of the fingers is likely to occur after these injuries, one is tempted to advise manipulation or passive movements with massage for the purpose of preventing or correcting the tendency to stiffness. There can be no doubt, however, that forcible passive movement applied in the early stages of such injuries can do incalculable harm. The ultimate stiffness of a finger-joint is the result of fibrosis round, and in, the capsule of the joint, and the degree of fibrosis determines the degree of stiffness. The degree of fibrosis is itself determined by the severity of the original injuries, the persistence of swelling, and the presence or absence of further injury. Each attempt at forced passive movement is a further insult to the injured tissues and, even if performed gently, must do harm. Excessive callus formation is the result of excessive movement of a fracture, and in the same way excessive movement will induce excessive fibrosis in an injured finger-joint. In the early stages there should be complete rest of the injured finger and active movements only of the uninjured fingers. So much is, I think, generally accepted.

A much more difficult problem is presented in the late case in which stiffness is already established. Is forcible manipulation of any value now? The results are varied. Painful reactions with swelling and stiffness follow the manipulation and the patient may be no better, or may even be worse, than before. Other cases may be greatly improved by a forcible manipulation and the manipulation may be repeated successfully, with a marked gain in finger movements which would not have occurred by natural means.

I think the criterion to be applied before attempting manipulation is that the patient has already reached the maximum natural recovery, and no further improvement is evident. Cautious manipulation at this stage of recovery may be of great value and rarely does harm. The fingers are bandaged in the flexed position after the manipulation and no active movements are attempted until the painful reaction has subsided—usually in a week or two. The manipulation may be repeated at intervals of three to four weeks.

The most extreme disability is produced by stiffness of the knuckle-joints in the extended position. If the fingers are splinted in this position or, if owing to the presence of unreduced backward angulation of a metacarpal fracture, the knuckle-joint is in a position of hyperextension, the lax capsule tightens and contracts, fixing the knuckle in this position. Correction of this deformity is best accomplished by continuous traction on a banjo type of splint with a palm piece in the cock-up position as a counter-point for the traction. The wire frame of the splint is bent down from day to day until it lies almost parallel with the flexor aspect of the forearm, and in this way increasing flexion of the knuckles is secured. The fingers can be unhooked from the splint a dozen times daily in order that the patient may practise active movements within the new range.

These conservative methods of splintage and manipulation will yield good results and are much more important than any operative measures for reconstruction or osteotomy of a malunited metacarpal fracture. It is my impression that severe disability is seldom the result of malunion or involvement of the extensor tendons in scar tissue, but is the consequence of stiffness of the fingers in the extended position.

In malunited fractures of the proximal phalanx, reduction of the angulation deformity by manipulative or open reduction must be the first consideration. When the deformity has been corrected the fingers should be allowed to recover from the stiffness naturally, to the fullest extent and then, if necessary, manipulative measures should be employed.

Section of Comparative Medicine

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Hepatitis and Jaundice Associated with Immunization against Certain Virus Diseases

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ABSTRACT.—(1) Among 3,100 persons immunized against yellow fever with virus and immune serum over a period of five years, 89 cases of jaundice have been traced.

(2) The symptoms are those of a hepatitis and closely resemble those produced by common infective hepatic jaundice, cases of which have frequently been noted as occurring in the same areas.

(3) The average period between the time of inoculation and the development of hepatitis is between two and three months.

(4) Attention is directed to the occurrence of hepatitis in horses, usually two to three months after immunization against the viruses of horse sickness and equine encephalomyelitis, and also after the injection of horse serum containing antitoxins against *Cl. welchii* toxins. Similar symptoms were observed, though to a lesser extent, in normal horses.

(5) The only factor common to the inoculated horses and men was the injection of homologous proteins, either in sera or in tissue extracts.

(6) The only theories which at present explain the observed facts are that either (1) a hepatotoxic virus is introduced with the virus inoculum or that (2) two factors combine to induce the hepatitis (*a*) a hepatotoxic substance present in the homologous serum or tissue extract injected and (*b*) an infective agent which, in the case at least of human beings, is probably the causal agent of common infective hepatic jaundice.

RÉSUMÉ.—(1) Parmi 3,100 personnes immunisées contre la fièvre jaune en cinq ans, 89 cas d'ictère ont été retrouvés.

(2) Les symptomes sont ceux de l'hépatite, et ressemblent de très près ceux de la jaunisse infectieuse ordinaire, dont on a souvent noté la prévalence dans les mêmes régions.

(3) La période moyenne entre l'inoculation et l'apparition de la jaunisse est de deux à trois mois.

(4) L'attention est attirée sur le fait qu'il existe une hépatite chez le cheval, survenant généralement deux à trois mois après l'immunisation contre le virus de la maladie du cheval et de l'encéphalo-myélite de chevaux, et aussi après l'injection de sérum contenant des antitoxines contre le Cl. welchii. Des symptoms analogues, mais à un moins haut degré, ont été observés chez des chevaux normaux.

(5) Le seul facteur commun à l'inoculation de l'homme et des chevaux est l'injection de protéines homologues sous forme de sérums ou d'extraits tissulaires.

(6) Les seules théories qui peuvent actuellement expliquer les faits observés sont: (1) l'introduction d'un virus hépatotoxique en même temps que la substance inoculée, et (2) la combinaison des deux facteurs suivants pour produire une hépatite, (*a*) la présence d'une substance hépatotoxique dans le sérum homologue ou dans les extraits tissulaires injectés et (*b*) un agent infectieux qui est probablement l'agent causatif de la jaunisse hépatique infectieuse, au moins chez l'homme.

ZUSAMMENFASSUNG.—1. Unter 3,100 während der letzten 5 Jahre gegen Gelbfieber mit Virus und Immunserum immunisierten Personen wurden 89 Fälle von Ikterus gefunden.

2. Die Symptome sind dieselben wie bei einer Hepatitis und gleichen denen einer gewöhnlichen infektiösen hepatischen Gelbsucht, von der zahlreiche Fälle in denselben Gebieten beobachtet wurden.

3. Zwischen Impfung und Auftreten der Hepatitis vergeht durchschnittlich eine Zeit von 2-3 Monaten.

4. Verf. erwähnt das Vorkommen von Hepatitis bei Pferden, die gewöhnlich 2-3 Monate nach Schutzimpfung gegen das Virus der Pferdepest und -encephalomyelitis sowie nach Einspritzung von Pferdeserum mit Antitoxin gegen *Cl. welchii* auftritt. Aehnliche Erscheinungen wenn auch leichteren Grades wurden auch bei normalen Pferden beobachtet.

5. Der einzige Faktor, den die Impfung der Menschen und die der Pferde gemeinsam hatten, war die Einspritzung von homologen Proteinen, in Form von Serum oder Gewebsextrakten.

6. Die einzigen Theorien, die derzeit die beobachteten Tatsachen erklären können sind 1. Einführung eines hepatotoxischen Virus mit dem Impfstoff; und 2. Zusammenwirken zweier Faktoren, die eine Hepatitis hervorrufen: (*a*) ein hepatotoxischer Stoff, der sich im homologen Serum oder in den injizierten Gewebsextrakten befindet, und (*b*) ein Infektionserreger, der zum mindesten beim Menschen wahrscheinlich der Erreger der gewöhnlichen infektiösen hepatischen Gelbsucht ist.

In a previous communication (Findlay and MacCallum, 1937) attention was drawn to the possible association of acute hepatitis with immunization against yellow fever: 52 cases of jaundice had then been traced among approximately 2,200 persons immunized against yellow fever during a period of four and a half years. Attention was drawn to the following facts: (1) The symptoms of hepatitis and jaundice did not come on for at least two months after inoculation and might be delayed for nearly seven months, although the majority of cases occurred two to three months after immunization; (2) the symptoms observed were very similar to those of common infective hepatic jaundice (epidemic catarrhal jaundice) and in two instances the hepatitis developed four weeks, the correct incubation period, after exposure to infection with common infective hepatic jaundice; (3) the occurrence of the jaundice was not directly due to an infection with the yellow fever virus.

In the present paper further details are given of acute hepatitis and jaundice in association with immunization against yellow fever, and in addition attention is directed to the occurrence of a similar syndrome in animals following immunization against two other virus diseases, namely horse sickness and equine encephalomyelitis, as well as against a disease of unknown ætiology—grass sickness.

Hepatitis and Yellow Fever Immunization

During the five years from November 1, 1932 to October 31, 1937, 3,100 persons have been immunized in this country against yellow fever. As is perhaps only natural with a new form of immunization, a number of early and late sequelæ have with confidence been attributed, either by the patients themselves or by their medical attendants, to the immunizing injections. The list of such sequelæ includes malarial attacks, scabies, herpes, interstitial keratitis, tonsillitis, chronic myocarditis, chronic interstitial nephritis, gastritis, duodenal ulcer, gall-stones, appendicitis, rheumatoid arthritis, acute mania, and suppression of the menses. In contrast to this variety of conditions, none of which shows any positive correlation with the preceding inoculation, is the occurrence of 89 cases of jaundice.

The symptoms in all these cases have been closely similar and have varied in degree rather than in kind. At first there is tiredness, loss of appetite, nausea, and occasionally bilious vomiting, often associated with a feeling of heaviness over the liver. The temperature may be slightly raised. After a period varying from two to three days to a fortnight, or more, the patient notes that his urine is dark-coloured and is told that the whites of his eyes and skin are yellow. His temperature is now normal and he begins to feel better; the loss of appetite and the jaundice may, however, continue for some weeks and, owing to the loss of weight and the mental depression induced, convalescence may be slow. Physical examination may reveal an enlarged and slightly tender liver and occasionally some enlargement of the spleen, though, since many of the patients are old malarial subjects, little importance can be attributed to this sign. The blood shows no change in the number of red corpuscles,

while the white cell count is either normal or reduced, with a relative increase in the lymphocytes. The van den Bergh test shows a delayed direct positive reaction and an indirect reaction which has registered as high as 29 units of bilirubin. The pulse is usually slow and the cardiac dullness may be increased to the right of the sternum. The urine contains bile and, on rare occasions, a trace of albumin. The stools in slight cases may be almost normal in colour but are more frequently clay coloured. It will be seen that the symptoms differ entirely from those of yellow fever but closely resemble those of common infective hepatic jaundice.

The average interval between the yellow fever immunization and the onset of jaundice has been between two and three months ; the shortest interval was thirty-six days, the longest just under seven months.

Cases have occurred in England, Egypt, the Anglo-Egyptian Sudan, South Africa, and the West African Colonies, while apart from the present series of cases, jaundice has been known to follow yellow fever immunization in South America, and in French Gabon.

The method first employed of immunizing human beings against yellow fever consisted in the injection of human yellow fever immune serum and a strain of yellow fever virus passaged in mouse brains : for injection this neurotropic virus was made up in normal human serum. Later, horse yellow fever immune serum for a time replaced the human immune serum though the virus component was still made up in normal human serum. The last 1,000 patients to be immunized received an attenuated strain of ordinary yellow fever virus grown in tissue culture but made up with normal human serum in order to preserve the virus. The amount of normal human serum injected never exceeded 0·275 c.c. Since August 1 all serum used has been heated at 56° C. for thirty minutes, but among the 627 persons immunized from August 1 to October 31, 13 cases of jaundice (2·07%) have been recorded. In addition to heating, the serum has latterly been obtained from healthy donors who have, so far as they know, never suffered from jaundice. Whatever the exact method of immunization, jaundice has continued to occur although it has been noted that the cases have tended to fall into regional groups.

It will be observed, however, that the only two common factors have been the injection of yellow fever virus and homologous serum.

Hepatitis and Immunization against Horse Sickness

The earliest report of acute hepatitis and jaundice associated with immunization against a virus disease, is that of Theiler (1919), who noted these conditions in horses that had been immunized against horse sickness in South Africa.

From the clinical symptoms observed, the syndrome was given the descriptive term of " staggers ", while pathologically the main feature was an acute necrosis of the liver, involving more especially the central portion of the lobules. Of 1,148 horses immunized against horse sickness, 27 or 2·2% developed staggers, mostly in from sixty-two to seventy-eight days after immunization, the shortest time being twenty-seven and the longest one hundred and sixty-five days. During the same period similar symptoms occurred in four of 160 normal horses which had not been immunized against horse sickness, although they were almost certainly " salted ", that is to say, immune to it. Of 1,411 Army horses immunized against horse sickness there was a mortality of between 4% and 5% and a few cases were also reported in non-immunized horses. In another series of 1,154 horses immunized on farms, 210, or 18%, of the animals, died with acute liver necrosis, while in the same region seven cases were reported in normal horses not experimentally immunized against horse sickness. Two animals observed in the Rustenburg district (a mare and a stallion) almost certainly contracted the disease from another horse suffering from " staggers ". Among the immunized horses, two of those affected had received only one injection of horse sickness virus, and two others only injections of horse

serum containing immune bodies against horse sickness virus ; the other horses had been injected with both horse sickness virus and horse serum containing horse sickness immune bodies. Unfortunately no indication is given as to whether the horse sickness virus was or was not suspended in horse serum, but in any case the virus was contained in tissues from infected horses.

Hepatitis and Immunization against Equine Encephalomyelitis

A similar history has recently been recorded from Montana, U.S.A. by Marsh (1937 [1] and [2]) where 5,933 horses were immunized against equine encephalomyelitis, either with immune serum alone or with mixtures of immune serum and equine encephalomyelitis virus. Subsequent symptoms were observed in 89 horses, and of these 79 died. Of the 89 horses developing symptoms, 81 had been immunized against equine encephalomyelitis while the others were, as far as is known, perfectly normal. The percentage of immunized horses developing the syndrome was 1·5 and the time interval between inoculation and the appearance of symptoms varied from thirty-two to ninety-two days, though in 90% of cases the interval was from forty to seventy days. The syndrome observed consisted of restlessness, muscular tremors, impaired vision, profuse sweating, and an icteric tint of the mucous membranes. There was no rise in temperature and no prostration, but death frequently took place in from twenty-four to forty-eight hours after the onset of symptoms. At the post-mortem examination the mucosa of the stomach was hyperæmic while that of the entire intestinal tract exhibited enteritis and hyperæmia. Microscopically the most important changes were noted in the liver, in which there was acute degeneration of the liver parenchyma in the centre of the lobules, with pigment deposition in the degenerated cells. The centre of the lobules also showed excess of red blood cells in the intralobular sinuses, more especially around the efferent vein, while at the periphery of the lobules in the region of the portal spaces, there was increased infiltration with round cells. The kidneys showed parenchymatous degeneration of the tubular epithelium with petechiæ in the cortex. No lesions were present in the brain or cord and the virus of equine encephalomyelitis was not recovered from the tissues. The immune serum employed was obtained from a number of different sources.

Dr. Marsh informs us (1938) that during 1937 no effort was made to immunize horses against equine encephalomyelitis in Montana. A considerable number of horses in due course developed equine encephalomyelitis but there was only one case of what he has called " the secondary disease " and that was in one of the few horses that had received equine encephalomyelitis horse serum.

Hepatitis and Immunization against Grass Sickness

The following unpublished facts we owe to the kindness of Dr. W. S. Gordon of the Moredun Institute, Edinburgh, who has generously placed them at our disposal.

As a result of finding *Clostridium welchii* toxin in the intestinal contents of horses suffering from grass sickness it was thought possible that the toxins of this bacillus might be the cause of death in this disease. In order to test the theory an antitoxic serum against this toxin was prepared and 617 horses on farms where grass sickness was prevalent were injected subcutaneously with 15 c.c. of the serum. 692 horses on the same farms were taken as controls. Symptoms began to develop in 30% of the inoculated animals, on an average fifty-six days after the inoculation, and consisted of œdema round the muzzle and, in some cases, mental involvement, the horses dashing through obstacles as if they did not see them. Forty-seven horses died, and in the few cases examined post mortem the liver was found to be necrotic. Somewhat similar symptoms, associated with œdema of the muzzle, are said to have occurred in three of the control horses, but the animals recovered. Subsequent attempts to produce the same syndrome in horses under laboratory and field conditions failed.

Possible Causes of the Occurrence of Hepatitis in Association with Therapeutic Immunization

From a consideration of the above occurrences it is possible to deduce three facts common to all :—

(*a*) In every case the inoculum contained homologous substances, either in the form of homologous serum or homologous tissue suspensions. Sometimes, however, the amount of homologous serum injected was small and it did not exceed 0·275 c.c. in the case of certain of those immunized against yellow fever.

(*b*) The period between the inoculation and the onset of symptoms was on the average from eight to twelve weeks.

(*c*) In the case of the hepatitis following yellow fever, equine encephalomyelitis and horse sickness, and probably also grass sickness, similar symptoms occurred in men or horses not inoculated.

Bearing these facts in mind, it is now possible to discuss possible explanations of the occurrence of the hepatitis :—

(1) *Coincidence.*—It was at first thought (Findlay and MacCallum, 1937) that the appearance of an occasional case of jaundice after yellow fever immunization was due merely to a chance infection with common infective hepatic jaundice. Nevertheless the wide distribution of the cases both in space and in time, and the finding that approximately 3% of those immunized have developed jaundice suggests a positive correlation. The occurrence of hepatitis in association with other forms of therapeutic immunization almost certainly rules out any possibility of pure coincidence.

(2) *Jaundice may be caused by the virus inoculated.*—The fact that jaundice has followed when no virus was injected, but only immune serum containing antibodies against either horse sickness or equine encephalomyelitis, rules out the possibility of a delayed reaction on the part of a specific virus. Further evidence that the syndrome is not due to a recrudescence of the virus infection may be summarized as follows :—

(*a*) Clinical symptoms and pathological changes : In *man*, these closely resemble those of common infective hepatic jaundice and differ from those of yellow fever in the almost complete absence of fever, the absence of headache and backache, the frequent paleness of the stools, the long continuance of the jaundice, the occurrence of a delayed direct van den Bergh reaction, and a high bilirubin content in the serum. Further, in the liver of a man who died twelve weeks after inoculation there were no lesions resembling yellow fever. In *horses* the symptoms are not those of either horse sickness or equine encephalomyelitis ; the lesions found in the liver and in the central nervous system of horses dying after immunization against equine encephalomyelitis also differ from the lesions caused by these two diseases. Marsh (1937 [1]) was unable to find any lesions suggestive of equine encephalomyelitis.

(*b*) Failure to obtain virus either from the blood, even after it has been diluted, in human cases of jaundice following yellow fever immunization, or from the central nervous system of horses after equine encephalomyelitis inoculation.

(*c*) Lack of increase in the yellow fever immune body titre of the serum during or after an attack : In persons who have had jaundice after immunization the immune body titre falls just as it does in other immunized persons, whereas in persons naturally infected with yellow fever the immune body titre falls much more slowly.

(*d*) Hindle (1932) failed to obtain yellow fever virus from the tissues of monkeys after the development of yellow fever immune bodies. An attempt to repeat these experiments on a considerable scale, using dilution methods, has completely failed to show the presence of virus in the tissues of immune yellow fever monkeys. The livers of rhesus monkeys killed from two to six months after immunization do not show any lesions suggestive of yellow fever.

(*e*) Development of jaundice in a woman following the injection of yellow fever

immune serum and neurotropic yellow fever virus, though at the time of the injection the patient was already immune, owing to a natural attack of yellow fever.

All of these observations oppose the suggestion that the yellow fever virus is the cause of the jaundice.

(3) *The jaundice may be an anaphylactic phenomenon*, due to some constituent of the homologous serum. Apart from the fact that anaphylactic phenomena very rarely attack the liver, it is not easy to determine what constituent of the homologous serum could be responsible for a sensitivity phenomenon. Two persons who had developed jaundice were injected intradermally with 0·01 c.c. of the original serum virus mixture with which they were inoculated, but they showed no evidence of skin-sensitivity. One person who had had jaundice has been reinoculated without again developing jaundice. The only possible line of approach to this problem from the point of view of sensitivity is that suggested by the work of Hughes (1933), who found that during the acute period of yellow fever a protein appears in the blood-serum. This protein, which is derived from some tissue breakdown product, is antigenic since, during convalescence, the serum contains a precipitin which will give a specific reaction with the original antigen.

(4) *Some hepatotoxic substance may be introduced with the immunizing inoculum.*—Since hepatitis has followed the use of immune serum alone, it would appear possible to exclude any toxic substance present in the virus inoculum. Although there has been no previous suggestion that homologous serum is in any way toxic, there is nevertheless an unexplored possibility either that it may be toxic to particular persons or that certain apparently normal sera may contain an hepatic antibody which damages liver cells, in the same way that an anti-platelet serum can be produced which has a specific action on platelets. The observations of Hughes (1933), to which reference has already been made, show that homologous tissue breakdown products can produce antibodies in the same individual: possibly these antibodies are toxic to other individuals. Experiments are at present being undertaken to investigate this question.

(5) *Jaundice may be due to some organism injected with the virus or serum.*—If some extraneous organism capable of producing hepatitis gained entrance to the virus or serum inoculum, it is one which will not grow aerobically or anaerobically on ordinary bacterial media and must almost certainly be a virus, since both the virus inoculum and the immune serum are passed through a Seitz filter. If the hypothetical virus were introduced with the yellow fever virus inoculum it must have been grown in tissue culture in association with the yellow fever virus. If the hypothetical virus is introduced in the serum it is necessary to postulate that (*a*) it is present in the sera of apparently healthy persons who have never knowingly suffered from jaundice; (*b*) it can withstand the addition of 0·2% tricresol and 0·2% ether for many months; (*c*) it can withstand a temperature of 56° C. for thirty minutes, and (*d*) the same or a very similar virus must gain entrance both to human and horse serum.

Thus although the presence in the serum of a hypothetical virus or viruses pathogenic for man and horses cannot be entirely excluded the evidence in its favour involves certain important assumptions.

This possibility is being eliminated by the use of another strain of tissue culture yellow fever virus which was first used for human immunization at the beginning of November 1937. Sufficient time has not yet elapsed to determine the effect of this virus on the incidence of jaundice.

(6) *Jaundice may be due to some intercurrent infection coming on as a result of lowered resistance.*—The last possibility to be considered is that the injection of homologous serum may, by reducing the resistance in some way, predispose to intercurrent infection. A classical example of one infection predisposing to another is of course the occurrence of herpes febrilis in association with lobar pneumonia. Many virus infections also predispose to, or are almost symbiotic with, bacterial infections,

as in the case of human and swine influenza, dog and cat distemper, and swine fever. It is, therefore, not impossible that the injection of homologous serum may in some cases predispose to an intercurrent infection and in the case of human beings there is a widely-spread disease—common infective hepatic jaundice—the symptoms of which closely parallel those of the jaundice following yellow fever immunization. Against this theory is the fact that many children have been injected with anti-poliomyelitic immune human serum and no case of jaundice has been recorded. Thousands of cattle have also been inoculated with anti-rinderpest homologous serum. In favour of the infective theory of post-inoculation jaundice may be cited the following facts :—

(i) The cases of post-inoculation jaundice almost always tend to occur in groups in regional areas, and careful question has elicited the fact that cases of jaundice have also occurred in the same areas, either in African natives or in Europeans in the case of yellow fever, or in apparently normal horses in the case of horse sickness and equine encephalomyelitis.

(ii) Common infective hepatic jaundice frequently occurs in man in small groups such as are found in schools, hospital wards, regimental battalions, and venereal and diabetic clinics (cf. Graham, 1938).

(iii) Theiler (1919) records instances in which the jaundice of horses associated with horse sickness was almost certainly spread as an infection. In two of our series of yellow fever post-inoculation jaundice cases, the patients developed jaundice exactly four weeks (the correct incubation period) after exposure to infection with common infective hepatic jaundice.

(iv) Medical officers appear to be more liable than others to develop yellow fever post-inoculation jaundice, since of 33 medical officers in Nigeria immunized against yellow fever eight developed jaundice.

(v) Common infective hepatic jaundice is especially liable to appear in venereal clinics where drugs such as neoarsphenamine or acriflavine (cf. Murray, 1930) are being administered. There is now considerable evidence to show that the arsphenamines, even in therapeutic doses, interfere with liver function, as shown by the increase in blood phosphatase (Lamb and Blakely, 1937), but jaundice only occurs in epidemic form when an infection is superadded. Other instances of synergic action between chemical substances and bacterial infections have been demonstrated experimentally. Unfortunately, in order to prove that, at any rate in the case of man, post-inoculation jaundice is due to the agent of common infective hepatic jaundice, it is necessary to transmit this disease to lower animals. Up to the present this has proved impossible for neither rhesus monkeys, whether normal or immunized against yellow fever, dogs, cats, ferrets, hedgehogs, rabbits, guinea-pigs, rats, or mice, have proved susceptible. We have also failed up to the present to confirm the claim made by Thune Andersen (1937) that common infective hepatitis of man is transmissible to pigs and is identical with the hepatitis met with in these animals.

Thus, although there is presumptive evidence that in the case of man post-inoculation jaundice is identical with common infective hepatic jaundice, absolute proof is not yet possible.

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Discussion.—Dr. WILBUR A. SAWYER (New York) said that the type of jaundice described by Dr. Findlay had not been seen in connexion with the present method of vaccination in Brazil; about 80,000 persons had already been vaccinated.

He pointed out that since November 1, 1937, when the strain of the virus employed had been changed, there had been no jaundice complications in Dr. Findlay's series. At that time he (Dr. Sawyer) had predicted that the trouble with regard to jaundice in that series had probably come to an end.

Dr. P. MANSON-BAHR said that it was only possible for him to argue upon the clinical aspects of this subject. He was now fairly confident that a condition—a definite post-inoculation hepatitis—did exist and that, moreover, it was quite distinct from epidemic infective hepatitis (or camp jaundice) to which reference had been made in the paper.

He had recently had the opportunity of examining two well-marked cases in detail. Both had been inoculated with tissue-culture vaccine on the same day, in October 1937, and both had developed jaundice on the same day—three and a half months afterwards. The symptoms in each case had been identical; the illness had run the same course and had lasted approximately the same time—two months—before recovery was established. This seemed to him more than a mere coincidence and he had also been able to interview others from West Africa who had also suffered from the particular complication and who had had the same experience.

It seemed to him unquestionable that the hepatitis was associated with the vaccine, which in some way exerted a gradual but delayed action upon the hepatic cells; that the process was intrinsically a hepatitis and it was not till the causal factor—whatever that might be—had been completely eliminated that regeneration of the hepatic cells was possible.

Clinically, the illness was characterized by the gradual onset of the jaundice, and was accompanied by nausea and anorexia. The liver itself was enlarged and tender, epecially over the lower border. There was no pyrexia; the pulse was slow and the usual accompaniments of jaundice, such as mental depression and pruritis, were noted. The fæces were not entirely colourless, as might be expected. The jaundice gradually deepened till about the third week, when the Van den Bergh readings were high; these were diphasic and gave readings as high as 27 units (indirect reaction).

Whilst the jaundice was apparent, the patients lost a considerable amount of weight (about 14 lb.), and recovery was established gradually. Restoration of the appetite appeared to be the first stage of the process.

On these grounds he argued that inoculation jaundice was a recognizable condition in some way connected with the pantropic yellow fever virus introduced into the body at the time of the inoculation.

Sir PATRICK LAIDLAW said that he would like to have information on two points: (1) What was the mortality rate, if any, in the cases in which jaundice developed? (2) Did liver function tests show any residual liver damage on recovery from the jaundiced state?

Dr. C. H. ANDREWES asked whether any liver function tests had been carried out upon persons who had been vaccinated against yellow fever but had *not* developed jaundice. Such tests might reveal that minor degrees of liver damage were common after vaccination, only the severer cases being detected clinically.

Dr. FINDLAY (in reply): said that the fact that no cases of jaundice had so far been notified among 1,100 persons immunized with another strain of yellow fever virus employed since November, 1937, suggested that some hepatotoxic agent, possibly the virus of infective hepatic jaundice, had been grown in tissue culture with the yellow fever virus. He was entirely unable to agree with Dr. Manson-Bahr's suggestion that there was any symptom or test by which one could distinguish this post-inoculation jaundice from infective hepatic jaundice. In both conditions there was a graduated series of cases, the mildest of which exhibited only a transient jaundice of a few days' duration. Post-inoculation jaundice had occurred after injection both with the neurotropic and the pantropic yellow fever virus.

There had, up to the present, been no mortality and liver function tests performed some months after recovery from the jaundice had failed to show evidence of residual damage. Routine bilirubin estimations carried out on sera from some hundreds of persons three or four weeks after yellow fever inoculation had not shown any evidence of liver damage.

Section of Epidemiology and State Medicine

President—Sir ARTHUR MACNALTY, K.C.B., M.D., F.R.C.P.

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A Historical, Epidemiological and Ætiological Study of Measles (Morbilli; Rubeola)

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DEFINITION

MEASLES is an acute specific contagious disease, probably caused by a virus, which invades the system via the respiratory tract. The period of incubation is from seven to fourteen days, and this is followed by a pre-eruptive period lasting about four days, during which time the patient has catarrhal symptoms, chilliness, sneezing, a cough, and running at the eyes and nose. During the pre-eruptive stage characteristic spots, known as Koplik spots, appear on the buccal mucous membrane.

The pre-eruptive period is followed by the characteristic blotchy deep mulberry red macular eruption which starts on the forehead and behind the ears and quickly spreads over the whole body. There is a rapid rise of temperature as the rash comes out, rapid respiration, bronchial catarrh, and congested mucous membranes.

In uncomplicated cases the temperature falls by lysis as the rash fades; slight branny desquamation of the skin occurs, and a faint mottled staining can usually be seen for some days after the temperature is normal.

The disease is not communicable in the incubation period but is highly infectious in the pre-eruptive stage, and the infection rapidly dwindles and is lost by the fourth or fifth day of the eruption.

HISTORICAL SURVEY

The disease cannot be recognized as such in any writings before Rhazes (d. tenth century). He gives an account of measles in his "Liber Continens" and states clearly that although there is a close affinity between smallpox and measles they are different diseases; smallpox being caused by "heat and putrefaction" in the fermented blood "acting in moisture" whilst measles is caused by a "vehement ebullition of the bile in the blood".

It is interesting to note that Rhazes, to support his views, says that he quotes from authorities who lived two hundred years before him. It may be inferred therefore that measles, as a separate disease, was also known to them. The views propounded by Galen (in his "Methods of Therapeutics", second century) as to the cause of disease and accepted as the theory of humoral pathology were the same as those subsequently enunciated by Rhazes to explain the cause of measles. A

contemporary of Rhazes—Isaac the Israelite—enunciated another and very curious hypothesis of its cause based on an older notion, namely, that measles was caused by the viciousness of the menstrual blood. According to this theory the noxious portion of the child's mother's blood was during pregnancy retained in the infant *in utero*; the mother therefore did not menstruate whilst carrying the baby. Sooner or later, however, the child had to get rid of this vice, and the process of its expulsion gave rise to the attack of measles. This hypothesis was apparently accepted by Thomas Willis (1660) who, in his treatise on medicine, couples smallpox and measles and refers to them as " mixed distempers ". The menstrual hypothesis was indeed an ingenious one, for it explained why every child suffered from measles and perhaps why many parents still think that every child must have measles.

Although the fact of infection generally was recognized for many centuries, measles was not accepted as an infectious disease until the sixteenth century when Jerome Frascator included it with other diseases like *variolae pestilentes febres* (enteric, influenza, and pneumonia), *febris quam lenticulas vel puncticulas aut peliculas vocant* (typhus) and *vere pestiferae febres* (plague) in his " De Morbis Contagiosis ".

In an English manuscript of 1325 the French " rugeroles " is translated by the word " maselas ", and in the " Book of Simples Englishes " by John Aderne, the French " rugoles " is translated by the word " maselys ". In a letter by Pace, Dean of St. Paul's, to Cardinal Wolsey (1518), the word " mezils " is used.

Even at this time there was still great confusion between smallpox and measles, for we find that Thomas Phare in his " Book of Children " (1553) writing of " small pockes and measils " says that " this disease . . . is of two kinds: varioli, ye measils; and morbilli, called of us ye small pocks ".

William Clowes, surgeon to St. Bartholomew's Hospital, in his " Proved Practice for all Young Chirurgeons " (1591) renders the word *variolae* by " measles "; and in (a schoolmaster) Levin's " Manipulus Vocabulorum " (1570) " Ye maysilles " is translated by *variole*. But by 1629 (at any rate in England) these two diseases are entered separately in the returns of deaths issued by the Parish Clerk, and in 1676 Sydenham in his writings clearly distinguishes between smallpox, measles, and scarlet fever.

The word " measles " apparently is of Teutonic origin—mas or maes, meaning a spot. There is another word " mesles " derived from the Latin diminutive *misellus*, a small miser, quoted in William Langland's " The Vision of Piers Plowman " (1362), and there it meant the leprous person. Later on the two words—" mesles ", the leprous, and " *maseles* " or " *measels* ", the disease we are now discussing, became confused, and finally were only used as the English equivalent of " morbilli ".

Up to the eighteenth century we find the words " morbilli ", " rubiolae ", " blacciae ", " lenticula ", " rossalia ", and " rossania " all mentioned in medical books, and there can hardly be any doubt that our disease measles was referred to by these words. The word " morbilli " originated from the Italian *morbillo*, so called to distinguish it from the more serious disease—the plague—which was known as " *il morbo* " (Hebra).

It might be inferred from this short historical summary that the early physicians were unable to distinguish between the various exanthemata which are now generally recognized. I cannot, however, bring myself to accept this conclusion, especially when I recollect that we still have to depend on the bacteriologist to distinguish for us between the various types of enteric fever, that the diagnoses of the food poisons have to be made by him, and that we are still in doubt whether scarlet fever embraces one or more specific entities.

May we not assume that the exanthemata, at any rate measles and smallpox, were so common in those times that they co-existed and often attacked the child at the same time? It must be remembered that, in pre-vaccination days, smallpox was largely a disease of children, and that measles or smallpox, and sometimes both

together, attacked the child population. Both were often so severe that they killed the sufferer in the prodromal stage of the disease. To-day in Bechuanaland, for instance, measles, which is still a very severe and indeed fatal illness in native races and communities, for long periods free from it, is said to accompany or follow smallpox, and the natives call it "the little smallpox". There is also the Arabian teaching already referred to, in which *variola* was the *morbus* proper and *morbilli* was its diminutive.

That measles was distinguished from smallpox in the time of Queen Elizabeth follows from the following dictionary definition: "It is a disease with many reddish spottes or speckles in the face and bodie, much like freckles in colour" (Baret).

It must be remembered that the art of medicine in those days was under the sway of authoritative Arabian tradition, and that the practitioner was then taught to make the illness of his patient fit the formula laid down, just as to-day original research is sometimes hampered by the dead hand of authority. Remember the well-known saying of William James:—

> "There are three stages in the history of every medical discovery. When it is first announced people say it is not true. Then a little later when its truth has been borne in on them, so that it can be no longer denied, they say that it is not important. Then, after that, when its importance becomes sufficiently obvious they say anyhow it is not new."

The ingenious and authoritatively accepted hypothesis of "the menstrual vice" as the cause in one way or another of the exanthemata prevented the physicians of that day from recognizing them as infectious diseases. However, we are told that "certain cases of smallpox, in which the pustules were wholly or partially represented by, or changed into, broad spots level with the skin, red or livid in colour, and in which hæmorrhages occurred from the nose, lungs, bowels, or kidneys", that is to say, cases of hæmorrhagic smallpox, were apt to be called by the name of "smallpox and measles mingled" (1670–1674). Sydenham's very clear description of the symptoms expressed in his account of the epidemics in London in 1670 and 1674 leaves no doubt whatever that he was describing cases of measles; his description of their behaviour is as clear and minute in all essential points as they would appear in a modern textbook of infectious diseases (Obs. Med. Book IV, Chapter 3, 1765). It may be of interest to note that, in the first half of the year 1674, London was affected by a measles epidemic causing 795 deaths, and in the second half by one of smallpox, causing 2,507 deaths. But in his analysis of the cases, Sydenham points out that the measles epidemic caused excessive deaths attributable to pneumonia and diarrhœa amounting to a total average of 468 deaths per week for the first six months, whereas in the smallpox months these deaths were only 349 per week. In other words, he hints that many of the deaths in the first six months must have been indirectly due to measles although they were registered under such headings as "convulsions", "teeth", "diarrhœa", and "consumption".

Dr. Robert Watt (1808) in his "Relative Mortality of the Principal Diseases of Children", made an analysis of the children under 10 years of age who died in Glasgow during thirty years. This analysis is one of the earliest and most memorable inquiries into vital statistics in this country. In his analysis Watt points out that, if child-life was first attacked by smallpox, a following epidemic of measles resulted in a lower fatality than if measles occurred first. He accounts for this by maintaining that, if a child recovered from smallpox, it was fortified against an attack of measles. And it would appear that he condemns vaccination as the direct cause of a higher mortality in measles. On these facts we should say that Watt's observations were correct but his conclusions wrong; that whether attacked by smallpox or measles the child who was likely to succumb was the delicate or weakly individual—the rickety, the marasmic, the lymphatic, or pre-tuberculous child—and that the healthy child was the one who was more likely to survive. If therefore smallpox preceded measles it would kill

off the weakly and leave the strong. When measles followed, as the weakly had already succumbed from smallpox, the mortality from measles would naturally be lower.

This is true to-day, for, as will be pointed out, the fall in mortality of measles has undoubtedly been due to improvements in child hygiene and, consequently, the reduction of the number of children predisposed to the complications which are so fatal to child-life.

Geography

With the world-wide reduction of smallpox by the introduction of vaccination, measles has now become, with the exception of influenza, perhaps the most prevalent and widely distributed of all infectious diseases. It is met with in all countries and all climates, temperate, sub-tropical, and tropical. Measles may be rarer in some countries than in others, but this is due not to latitude but rather to the accident of their isolation, commercial or otherwise, from those densely populated communities in which the disease is endemic. On the whole it is more common in temperate climates, but that is due to the same cause, namely, that the densely populated and industrialized communities happen to live in temperate climates. When and where measles is accidentally imported into those isolated communities from which it has for some time been absent, it rages with great violence, attacking a large proportion of the population and producing a high death-rate, until it exhausts all susceptible material, and it may then disappear entirely from that community until it happens to be reintroduced. In this respect it follows the usual rules of epidemiology already known to and enunciated by Hippocrates.

As stated, measles is endemic in densely populated centres. In London, and in other cities, both in this country and on the Continent, it recurs in epidemic form at regular intervals which vary from two to seven years.

In less populous areas its general distribution varies, and epidemics occur at irregular periods. In closed communities, like preparatory and public schools, it may be absent for many years, but when it does break out it is usually associated with serious complications and incapacity.

Measles is essentially a disease of childhood. For instance, in London it is found that most children have been attacked before their 7th year, and therefore, so far as the elementary schools are concerned, it is a disease of infants' departments and is of no significance in senior departments.

In one of the first investigations carried out in London elementary schools, Dr. C. J. Thomas showed that measles did not become epidemic in a school or district until the susceptible elements reached 40%, that the epidemic raged until the susceptibles were reduced to a figure below 20%, and that the epidemic then died down. The 20% of children who were not attacked apparently developed a transient immunity, for they were found to be susceptible by the time the next epidemic occurred.

In London these epidemics recur regularly every two years, beginning in the late autumn, reaching their highest incidence in the winter or early spring—usually February or March—and exhausting themselves by May or June.

The 40% susceptible material in the community which is necessary to start an epidemic outbreak is made up of the susceptible children who have been admitted to school since the previous epidemic, together with that proportion of the 20% of susceptibles who escaped an attack during the previous epidemic and have again in the interval become susceptible to the disease.

This process of developing immunity in one epidemic, to lose it again before the onset of another, is now a well-recognized factor, and has been experimentally demonstrated in the field-work of many epidemiologists, notably by Professors Greenwood and Topley. It was known to the ancients and mentioned by Hippocrates in his writings on Epidemics (470 B.C.). The process is possibly one in which the person

receives repeated subliminal doses of the infection, incapable of producing the disease but enough to stimulate the organism to put up sufficient resistance to infection. When the immediate need for resistance disappears, the stimulus fades into the background and the person once again becomes susceptible.

The Registrar-General in his report for 1891 pointed out that :

> "When there has been a severe outbreak in any year in a given area, it will be found that the returns of the next year show a subsidence in the area itself, but an extension in the adjoining districts; another year, and these districts are also comparatively free, while a wider circle of surrounding districts has become infected."

In the same report attention is also drawn to the fact that high minimum rates of measles mortality are usually found in large populous areas, without breaks in the population, and that low minimum rates are apparently associated with populations broken up into detached groups "since the infection may, under such circumstances, fail to be conveyed from one group to another, in which case it may die out for a season". This actually does occur in isolated regions such as the Hebrides, the Shetlands, &c.

The occurrence, on the other hand, of high maximum rates is due to bad sanitary conditions, or gross carelessness, or both. There is no doubt that the advances made in public health both as regards housing improvements, ante-natal and post-natal care of mothers, and greater attention to the feeding and care of children, have jointly contributed to the continuous fall in the death-rate of measles.

While, as already stated, measles is found in all latitudes, there is reason to believe that it is milder and more benign in temperate climates than elsewhere.

The season at which measles epidemics prevail varies greatly in different parts of the world. Severe epidemics have been reported as occurring at all seasons. In temperate countries they are more frequent in the colder than in the warmer months. Severe epidemics have, however, been reported in the middle of the summer in such countries as Spain and south Russia. Measles in London has become more or less stabilized. Usually, as already stated, the biennial epidemic begins at the end of October, but its effect, as regards both incidence and mortality, does not become appreciable until the middle or end of the following January. Both then increase rapidly, to reach their maximum in April, or early in May, and then there is a rapid fall until the epidemic exhausts itself by the end of June. From records published by Harman and Perkins this appears also to be true in the U.S.A., in Australia, and in South Africa, though in the two latter countries the months are reversed.

Neither the character of the soil, nor the degree of elevation above sea-level, nor the nearness to or distance from the sea appears to have the least influence upon the disease. In its relation to race, measles has no prejudices; all races are susceptible to it and in all it is a disease essentially of childhood.

Measles is one of the most infectious of all the infectious diseases. It is spread by the movements of infected persons who, as already stated, are highly infectious long before the rash appears, and the disease is spread by "droplet infection".

The intensity of different epidemics varies even in communities where the disease recurs at regular periods.

The severity and fatality of the cases depend on the prevalence, associated with the disease, of influenza, pneumonia, and streptococcal and other infections, just as in the past they depended on its association with smallpox. It will be noted that the mortality curve for measles follows closely that for bronchopneumonia.

Variability in the severity of outbreaks has been recorded in London and other English towns from time to time. In communities which have been long free from it, measles may become widespread, severe, associated with a variety of complications, and produce a very high mortality. This may be ascribed to many causes, some preventable and others possibly not. In the preventable group of causes are gross

ignorance as to how to limit the spread of the disease and to treat those suffering from it, exposure owing to lack of suitable housing and clothing, neglect of medical aid and nursing care, and gross insanitary conditions leading to secondary infection in persons whose resistance has been lowered by measles. We have come to appreciate how mass infection introduced into a susceptible community tends to raise the virulence of the infecting agent.

Amongst the apparently non-preventable causes, at any rate, in so far as any particular epidemic is concerned, is the condition of persons already weakened by previous neglect or disease. It is the tuberculous, the pre-tuberculous, the lymphatic, the bronchitic, the marasmic, and the badly-fed child that measles kills.

There have been numerous epidemics in which the mortality was for one cause or another excessively high, such for instance as the epidemics : (1) Introduced into the native population of the Amazon (1749). (2) In Estonia (1829). (3) Amongst Indians of Hudson Bay territory (1846). (4) Introduced by the white man into the Hottentot community of the Cape (1852). (5) In Tasmania (1854 and 1861). (6) In Mauritius (1874). (7) In the Fiji islands (1875) when between one fifth and one quarter (calculated at about 20,000 persons of all ages) of the population died from measles or its consequences. (8) Amongst the women and children in the Boer concentration camps in the South African war (1900–1901)—terribly fatal in its character. These women and children were brought together out of kindness, to prevent them from dying from starvation, but epidemic measles instead of hunger carried them off in their hundreds. This mortality was due entirely to lack of proper treatment, care and attention on the part of the mothers of the affected children and the women placed in charge of the camp.

Measles is a disorder in which the lightness or severity of the cases depends essentially upon the care and attention bestowed upon the individual patients. When, therefore, it breaks out in circumstances where proper care and attention are unobtainable or lacking, or where ignorance and neglect exist, it becomes a very alarming and deadly disease. Measles occurring during war-time becomes a serious disease. Examples of outbreaks at such times are on record and it has been shown that the causes of its deadliness under these conditions were the same, namely, improper care and attention, and that death was not due to the severity of the disease itself but to want of shelter, proper food, and medical and nursing attention which predisposed the patient to one or other of the fatal complications.

Such, for instance, were the outbreaks of measles : (1) In the National Army of Paraguay in the war with Brazil in 1865. (2) In the Confederate Army of America in 1866. (3) In the French Garde Mobile during the Siege of Paris in 1871. (4) During the last war, amongst recruits from the distant islands stationed at various training depots.

Ætiology

As already stated, measles ranks as one of the most highly infectious diseases, and in that respect must be placed in the same category with chicken-pox and smallpox.

The disease is characterized by signs and symptoms which cannot very well be misconstrued. Of the exanthemata, it is one of the most constant as regards its progress and development, from the instant when infection takes place through its periods of incubation, invasion, establishment, and cure. The attack is followed very rapidly by the development of a strong and lasting immunity, and by inference, the rapid elimination and disappearance of the infecting agent—the virus. This virus, as we know by experiment, is present in the blood of the sufferer during the period of invasion and perhaps up to the second day of the disappearance of the rash ; thereafter it is irrecoverable from the blood and rapidly disappears.

It is now known that an immunity due to the development of specific antigens rapidly takes place in the body tissues and is present in the blood of the patient soon

after the stage of convalescence, and that convalescent measles serum obtained from such a person may be used either to prevent an attack or to modify the disease in a person already infected with and incubating it. These antigens must therefore have a specific germicidal effect on the virus of measles and be responsible for the early loss of infectivity of the patient suffering from the disease.

Infants at the breast and up to 9 months old have a high resistance to infection, possibly due to antigens derived from the mother, a suggestion which would seem to be confirmed by the presence of this antigen in placental extract. Infants from 18 months to 2 years of age, on the other hand, are highly susceptible to measles and this susceptibility exists till about the 5th year, after which it diminishes.

As the ages 1 year to 5 years of a child's life are also those during which it is susceptible to those diseases which complicate measles, the mortality from measles is significant at those ages. The complications which are prone to attack the child are bronchopneumonia, ophthalmia, otitis media, diarrhœa. Measles, therefore, is a serious and dangerous disease for the pre-school child, and all preventive measures must aim at protecting the child at those ages. A child attacked should receive proper care and attention, and if these cannot be obtained in the home it is far better for the child to be admitted to a fever hospital where it can be treated as far as is possible under open-air conditions.

Bacteriology of Measles and Production of Experimental Measles

The cause of measles is as yet unknown ; but the results obtained in connexion with the production of experimental measles, whether in monkeys or in man, strengthens the view that the causal organism is a virus.

Inoculation of human beings with blood of patients ill with measles, even when very small quantities are used, will produce measles in the inoculated persons. This was first demonstrated by Francis Home, who, inspired by the successful results obtained by inoculation against smallpox, then newly introduced, took the blood of a patient in the eruptive stage of measles and applied it to the arm of a child in the same way as vaccination. The child developed an attack of measles in a mild form. This experiment is recorded by him in his " Medical Facts and Experiments " published in Edinburgh in 1759. Similar experiments have since been carried out by others with like results.

Herrman (1915) attempted to produce a form of active immunity in infants whilst still at the breast. As the child at the breast is assumed to be immune, he concluded that if, by inoculation with the virus, the child did develop the disease, it would be in a mild form. He therefore instilled into the nares daily doses of secretions which he took from measles patients. It was soon demonstrated that this experiment, though a forward step in the right direction, was unsafe.

More recently, investigators who have produced experimental measles in children have come to the conclusion that, in those in whom they succeeded in developing an attack, the symptoms produced by acquired measles were in no way different from or milder than those in cases developing the disease in the usual way. It may be assumed, therefore, that little or no progress can be made until the virus of measles has been isolated in pure culture and a vaccine prepared for active immunization.

In addition to the hæmolytic streptococci of many strains, invariably present, and the pneumococci which, as we now assume, are already present in a child exposed to measles and are responsible for the complication from which the child may subsequently suffer, Ruth Tunnicliff (1918) isolated and grew in pure culture a diplococcus (known as the " Tunnicliff diplococcus " or the " Greencoccus ") from the mucous membranes and blood of measles patients. As opsonins and other specific bodies were present in the blood of patients who had measles, Heklower concluded that this coccus had some significance in an attack of measles. But Park, Williams, and others

(1927) showed that the tests employed by Tunnicliff and Ferry and Fisher were of no value in establishing this coccus as the cause of measles.

Anderson and Goldberger (1911) carried out a series of experiments on monkeys to obtain, if possible, knowledge which might be of use in the prophylactic inoculation of humans against measles. They soon proved that monkeys, like men, are susceptible to the virus of measles ; that, when injected with blood from persons ill with measles, they developed an illness after from six to eight days which, as regards symptoms and reactions on the tissues, resembled human measles even to the extent of producing Koplik spots, leukopenia, and a subsequent desquamation. Again, they showed that the disease could readily be transmitted from monkey to monkey, by the usual methods of contact infection, by blood injections, and by transmitting the secretions of the mucous membranes ; and they proved conclusively that once they have suffered from an attack monkeys are immune against further attacks. Having established these facts they next attempted to produce a vaccine which could be used for prophylactic inoculation ; this they did by passage through monkeys, both in pure form direct from the sick animal and, also, by previously subjecting the virus to a variety of physical and chemical influences. They found that repeated transfers of blood from monkey to monkey resulted in an attenuation of the virus of measles to such an extent that it failed to induce the disease experimentally at the eighth transfer. Similarly, when passage of measles from monkey to monkey by contact was employed, the infection ultimately failed to infect.

The experimental work on monkeys by Anderson and Goldberger therefore led to no conclusions. It is still obscure why the measles virus lost its infectivity, and so it leaves the question of prophylactic vaccination against the disease still unsolved. But as success has already been obtained in such diseases as smallpox, distemper, and rabies, it is quite possible that this will before long be the case as regards measles.

Characteristics of Measles Epidemics in Europe and America

Measles is a disease which is well known and endemic in all European countries and on the Continent of North America. Its epidemiological aspects have been the subject of much study ; but this study has of necessity been incomplete as records of epidemics are very scanty. In England and Wales as a whole the disease was notifiable from 1915–1919. Notification by the medical practitioner was restricted to the first case in the home, the duty of notifying succeeding cases being placed on the parent.

Except in Denmark, and in New York, measles has not been notifiable long enough to afford sufficient information to permit of a comprehensive study of the disease in all its epidemiological aspects. A comparative study of its mortality has, however, been possible, and from this a fairly adequate knowledge of the behaviour of the disease has emerged.

In most temperate climates the disease is most prevalent in the winter and spring months, though summer epidemics have from time to time been recorded, as already stated, in the Iberian peninsula and certain other countries. In all these countries the disease is endemic and develops epidemic cycles, but each country seems not to affect the other as regards the spread of infection.

Taking the periods of maximum and minimum mortality as the best index of its prevalence it appears that the rate of spread under different conditions varies considerably, being more rapid in countries where the population is more or less evenly distributed and not collected in various centres.

The mortality curve has sharp fluctuations, the sharpness varying according to population distribution, but in every case a phase of high mortality is immediately succeeded by one of low mortality. This phenomenon tends to confirm the theory that immunization of the susceptible community is brought about on a large scale

by epidemics, and that the next epidemic will only occur when the susceptibles have increased to a sufficient number.

Season undoubtedly has a powerful influence on mortality. Except in the rare summer epidemics the most constant factor is the period of low mortality, which is September in most temperate countries, whilst the period of maximum mortality varies somewhat according to latitude. In this country it is in April, in the northern States of the U.S.A. it is in May, but in the southern States it is six weeks earlier.

Latitude also has an effect on the mortality of measles, but whether this is due to temperature, moisture, sunlight, or other unknown factor, has still to be demonstrated.

In this country severity of disease, or predisposition to complications, as shown by mortality, seems to go with latitude. As the table indicates, mortality is highest in the North and Midlands and lowest in the South. Whether this must be attributed to latitude or to density of population or industrial conditions remains still to be explored. But it must be remembered that measles, as such, does not kill the sufferer, deaths being invariably due to the complications following in the wake of the disease, the most important being bronchopneumonia.

Bronchopneumonia, apart from measles, has its maximum mortality in March and its minimum in August ; it is a disease very fatal in the young and is associated with the prevalence of the hæmolytic streptococcus and the pneumococcus, which, naturally, are more prevalent in industrial and urban areas with overcrowded and insanitary conditions. High mortality in measles may possibly occur in those persons who are harbouring these germs when they are invaded by the infection of measles, for the mortality of measles follows in the wake of, and does not coincide with, that of bronchopneumonia.

The parallelism of these mortality curves is very close if we compare the deaths for the ages 0–15 and even closer for the ages 1–4 years.

Incidence and Mortality

The following summary is taken from Creighton's book : During a full half century of registration (1801–1851) in all England and Wales the incidence of measles has fluctuated somewhat from year to year, but the disease has always remained one of the notable causes of deaths amongst infants.

In the decennial period 1871–1880, the annual average death-rate of measles was 377 per million living. In the next decade 1881–1890 it rose to 441. Most deaths during these periods were recorded from May to July, owing to the greater number of attacks in summer and not to the excessive fatality of the disease at that season.

From 1845–1874, it appears that the deaths touched a higher point in mid-winter (November–January) than in the summer, a fact which may be readily accounted for by the injurious effects of the town air in winter upon a disease which is largely one of the respiratory organs.

Most of the deaths from measles fall at present upon the ages from 6 months to 3 years, just as they did when the deaths were comparatively few from 1768–1774.

Deaths of adults, which were not altogether rare in the first great epidemic of modern times in 1808, are seldom heard of at present, for the same reason that adult deaths used to be uncommon in smallpox, namely, that the disease is contracted by almost everyone in infancy or childhood. Although the deaths from measles sometimes reach large totals, yet it is the common experience of practitioners that a strong or healthy child rarely dies of measles, and that the fatalities occur amongst the infants of weakly constitution and especially in the numerous families of the working classes in the most populous centres of mining, manufactures, and shipping.

These facts, taken from Creighton, give us an account of the incidence and death-rate of measles in England and Wales during the last century. It will be seen that

measles was then, as it is now, a serious disease, providing a high mortality, affecting chiefly the younger members of the community—but not invariably so, for on occasions there were indications that mortality occurred even amongst adults.

As far as London is concerned, there has been a definite reduction, since the ten-years' period 1891–1900, in the death-rate of measles, and this is more pronounced in character since the ten years' period 1911-1920, as the following figures will show :—

Death-rate per million of population—London.

		Males	Females
1851-1860	...	578	493
1861-1870	...	625	526
1871-1880	...	558	463
1881-1890	...	693	582
1891-1900	...	631	539
1901-1910	...	486	398
1911-1920	...	417	308
1921-1930	...	192	146
1931-1932	...	128	88
1933-1934	..	130	96
1935-1936	...	85	61

It will be noted that the mortality is invariably lower in girls than in boys.

Again it will be observed that the big decline in mortality began in 1920 and has continued ever since. This drop in mortality is sometimes ascribed to the falling birth-rate. This cannot be the case, for the number of measles cases reported from the schools during every biennial epidemic remains the same ; that is to say, the incidence of the disease amongst children remains the same, but the actual number of deaths each year must be ascribed to the general improvement in child health which has come about by legislation and education. We no longer see, in the same numbers, children who are tuberculous, rickety, debilitated, or marasmic, or who suffer from those deficiencies which lead to complications which are the causes of mortality in those attacked by measles.

This material improvement in the health of children must be attributed to the better attention and care given to mothers and children as a result of various enactments. These enactments have enabled local authorities to provide means for improving the health and vigour of children and to appoint officers, such as health visitors, maternity and child welfare doctors, and school doctors, to enforce them, and generally, by education, parents and teachers have learned that measles is a dangerous and destructive disease in the young, more especially in those who have previously been injured by disease or neglect.

The introduction of a system of school medical inspection by the London County Council in 1900 was undoubtedly responsible for drawing attention to the many defects which existed in children attending school, and at the same time made it possible to control the spread of infection in school. In fact, soon after the inception of school inspection, an investigation as to the behaviour of measles in schools was carried out by Dr. Thomas (to whom I have already referred) and Dr. Davies, the Medical Officer of Health of Woolwich, in which exclusion of susceptible children from infants' schools was tried with the view of controlling the mass spreading of the disease. This experimental exclusion of contacts, varied in degree from time to time, has been carried out and carefully controlled during every epidemic in London since 1900. The steps taken to control measles epidemics in London have been attended with success, for they have undoubtedly been responsible, if not for preventing epidemics, at any rate for slowing their progress through London. One of the causes of the lowering of the death-rate from measles is that both parents and teachers have come to recognize the disease as a serious one. The findings, in the several reports on

the epidemics, played an important part in securing the enactment of the Maternity and Child Welfare Act 1918—whereby local authorities were empowered to appoint health visitors, and to provide district nurses—and drew attention to the need of admitting selected cases of measles to fever hospitals. This control of measles in schools has been brought to a high standard of efficiency, for during each biennial epidemic there is now a complete co-ordination of forces between, on the one hand, the London County Council as the school authority through its teachers, school doctors and school nurses and attendance officers, and, on the other hand, the Metropolitan Sanitary Authorities through their Medical Officers of Health, health visitors, and district nurses. These co-ordinated agencies now deal with children in school, at home, at play, whether as sufferers, as contacts, or as those who should be protected against infection. Children suffering from measles who cannot be satisfactorily treated at home, whether owing to overcrowding, insanitary arrangements, or to want of medical and nursing attention, are now admitted at as early a stage as possible to one of the fever hospitals, where they are nursed back to health under open-air conditions. Their removal to hospitals from overcrowded homes also prevents the disease from attacking the younger members of the family who are not as yet attending school.

Legal Enactments

The following Acts, all placed on the Statute Book since 1900, viz. :—

Midwives Acts, 1902, 1918,
Medical Inspection (Examination and Provision of Meals) Act, 1907,
Education Act, 1921 (which repealed the last-named Act, the provisions of which it re-enacted),
Notification of Births Act, 1907,
Notification of Births (extension) Act, 1915,
Maternity and Child Welfare Act, 1918,

have, in one way or another, directly or indirectly, played a part in the reduction of the mortality from measles in the child community in so far as they have resulted in the lessening of nutritional diseases.

Gradually, the more common factors contributing to death from measles are disappearing. On the other hand there are indications of an increase in a previously unknown complication of measles, viz. post-measles encephalitis. The ætiology of this disease is still unknown, but it is a very fatal complication.

As a result of school medical inspection and attendance at child welfare centres, teachers and parents have learned, as already stressed, that measles is a disease particularly dangerous to children of pre-school age ; that needless exposure to infection, especially of the young child, should be avoided ; that patients, for their own sake and to prevent risk to others, require isolation and to be kept in a well-ventilated room ; that the best treatment to prevent complications is the open-air method, and that consequently a child is better in hospital than at home ; that the causes of death are the complications following on measles and not the disease itself. The danger lies in the presence and spread of the hæmolytic streptococcus, the pneumococcus, and the diphtheria bacillus. This fact is now so well established that in the infectious hospitals of the London County Council it has become a routine method of treatment to give each child with measles a prophylactic dose of diphtheria and scarlet fever antitoxin on admission.

Periodicity of Measles Epidemics

This subject was brought very prominently before this Society in 1918, by the late Dr. Brownlee. In his contribution, which must have entailed a great amount of

calculation and time, Brownlee demonstrated, by means of statistical analysis and periodigrams, that, in London, measles had come to behave in a static way, and had a recurrent periodicity which could be accurately represented mathematically.

His periodigrams clearly indicated to him that there were two types of measles existing in London, one north of the Thames with a recurrent periodicity of ninety-seven weeks, and the other south of the Thames with a recurrent periodicity of eighty-seven weeks. This theory of periodicity was based on evidence, previously obtained and presented to the Royal Society in a paper on the behaviour of tuberculosis. The existence of one kind of age-distribution of mortality from phthisis in Cornwall and of two other kinds in Ireland and in London led Brownlee to believe that there were three strains of tubercle bacilli producing three types of phthisis, viz. the " young ", the " middle-age ", and the " old-age " phthisis in these places. Similarly, his study of measles led him to believe in the theory of the continuous variation of the germ of measles, governed by physico-chemical laws. He was of the opinion that these changes could, as it were, be studied *in vitro* and therefore apart from environment.

Dr. Brownlee said : " Of periodicities in infectious diseases two explanations are possible . . . these two explanations have very different bases. In the one the infecting organism is the main factor. In the second, the conditions of the people." He went on to say : " Of course, these theories are not mutually exclusive ; the point to be determined is their relative importance. My opinion is strongly in favour of the first hypothesis."

The late Sir William Hamer, in a very able paper, went over the whole ground of Brownlee's hypothesis. With data prepared for him by Mr. B. E. Spear (of the Statistical Section of the Public Health Department, London County Council), he showed that Brownlee's conclusions did not hold, and that such periodicity of measles as exists could very readily be explained from the point of view of environment. Hamer pointed out that prior to 1870, the peak periods of measles mortality actually occurred in mid-summer, and that since that time the periods between predominant " peaks " in successive years had decreased generally from approximately one hundred and eight weeks in the forties to a minimum of about eighty-eight weeks late in the eighties, and thereafter had remained, roughly speaking, about one hundred and four weeks in recent years ; in fact, that the periodicity of measles was not static as Brownlee asserted. Hamer further stated that there was abundant proof that variations in periodicity were directly associated with alterations in environmental conditions. Of these, decreased aggregation of susceptibles and activity as regards the putting into operation of those preventive measures already referred to, had been chiefly responsible in affecting the behaviour of measles during the last fifty years.

Firstly, as regards the number of susceptibles, the birth-rate reached a maximum in the late eighties and has been steadily declining until the last year or two. Secondly, as to preventive measures, these were first seriously undertaken some twenty years ago and an appreciation of the importance of these measures by teachers, parents, and local education authorities has grown steadily since that time. Thirdly, the carrying out of measures dealing generally with the health of both mother and child has almost eliminated such conditions as marasmus, malnutrition, rickets, &c. Fourthly, these measures tend to a greater appreciation of an open-air life and the avoiding of all unnecessary exposure of the younger children to infection.

The operation of all these factors combined serves to explain the behaviour of measles in London ; firstly, in the shortening of intervals between successive epidemics in the late eighties, with a gradual tendency to the lengthening of the interval subsequent to that ; secondly, in bringing about, through the preventive measures developed in the early years of this century, the curtailment of each individual measles epidemic, with a consequent increase in the accumulation of susceptible persons

which resulted in the unusually explosive epidemics of 1911 and 1920. The regular series of biennial explosions of measles in London can be explained by the fact that the metropolis, by reason of its parts being so closely linked together by its various means of communication, now acts as one large magazine of susceptible, and so of explosive, material. When, therefore, measles is introduced into this magazine it leads to one short explosion which burns up the susceptible material as if by one large sheet of flame which, epidemiologically, is not instantaneous, but from start to finish takes about six months to complete.

Hippocrates (470 B.C.) in his "Treatise on Air, Water and Places" remarks on the constitutional tendencies of various populations in Europe and Asia, which when once formed, were perpetuated by heredity. Hippocrates had a wide conception of the facts of disease and prepared the way for the scientific study of life. He drew attention to the intermittency of epidemics and so may be called the father of the periodicity of infectious disease. His theories were, centuries later, confirmed by writers such as Sydenham and Graunt (National and Political Observations upon the Bills of Mortality, London, 1662) and in more recent times they have been proved experimentally by Professors Greenwood and Topley (1923, 1925).

In their more recent work ("Experimental Epidemiology", 1936) Greenwood and Topley summarize the knowledge gained by the various methods of epidemiology employed (descriptive, statistical, bacteriological, and immunological) and conclude that, after all, questions in epidemiology can only be answered by finding out what really happens in an infected herd, and not by deducing what might happen from our knowledge of what occurs in individual hosts. They state :—

"Our observations, and the interpretations that we have placed upon them, are in general accord with the view expressed by Hamer (1919) that the periodicity of such an epidemic disease as measles is probably due to periodic changes in the constitution of the population exposed to risk, leading, after each epidemic wave, to a gradual re-accumulation of susceptibles. These natural epidemic waves are not the minor fluctuations of our mortality curves, they correspond rather with the widely spaced waves observed with very slow rates of immigration, or with the effect produced by adding susceptibles to the population surviving from an epidemic prevalence. In the natural world, the re-accumulation of susceptibles is by births rather than by immigration; but there are specialized herds, such as schools in general and boarding schools in particular, in which the immigration of non-immunes term by term is probably a decisive factor in determining the course of events. . . . This ever-varying state of the immunological constitution of the herd is the main factor determining the intervals at which the epidemic waves of such an endemic epidemic disease as measles will occur."

As regards the mechanism by which this immunological constitution is determined they say :—

"We regard sub-lethal or latent infection as the essential factor involved in the immunization of any human herd."

Stocks, in his paper (1928), says that at the end of an epidemic of measles quite a number of children are immune, without suffering from the disease, but that a large proportion of these lose their immunity again in a year or two and so are added to the number of susceptibles amongst whom the disease may spread in the next epidemic.

In spite of the fact that measles in this country is an endemic disease, there are quite a number of isolated communities where it is non-existent, and when it is accidentally introduced it behaves like a new disease and attacks the susceptibles in that closed community until they are exhausted, and then it disappears. At the other extreme is an urban community, like London, where the disease is endemic and where the conditions of spread have become such that the disease recurs almost

like clockwork every two years ; one can almost predict the very week in November when the disease becomes epidemic and begins to spread from district to district and school to school.

Between these two extremes one meets with a variety of herds, some in which the disease recurs in epidemic form at irregular periods varying between two and seven years.

Amongst the former are certain fairly isolated rural communities and also our public and preparatory schools, where the scholars live a more or less sheltered and carefully guarded life. The members of these different herds are all of the British

TABLE I.—COUNTY OF LONDON: MEASLES DEATHS AND DEATH-RATES PER 100,000 LIVING IN TE

Males

Period	All ages	0 –	1 –	2 –	3 –	4 –	0–5	5 –	10 –	15 –	20 –	All a
1851-60												
Deaths	6,976	1,212	2,595	1,461	798	427	6,493	412	38	8	25	6,790
Rate	57·8	317·0	806·0	453·5	256·8	142·6	396·7	30·5	3·2	0·7	0·4	49·3
1861-70												
Deaths	8,852	1,715	3,451	1,890	906	436	8,398	398	24	7	25	8,486
Rate	62·5	376·0	894·4	492·9	242·2	121·0	428·6	24·7	1·7	0·5	0·3	52·6
1871-80												
Deaths	9,265	2,080	3,685	1,661	839	461	8,726	468	29	9	33	8,682
Rate	55·8	396·8	806·0	367·8	191·4	108·0	379·7	24·6	1·7	0·6	0·4	46·3
1881-90												
Deaths	13,119	2,756	5,074	2,389	1,306	774	12,299	757	34	6	24	12,330
Rate	69·3	501·9	1,033·7	478·3	271·7	164·6	494·0	34·9	1·8	0·3	0·2	58·2
1891-1900												
Deaths	13,085	2,939	5,404	2,197	1,239	696	12,475	558	20	7	25	12,484
Rate	63·1	536·3	1,106·5	437·0	253·8	146·1	498·3	24·8	1·0	0·3	3·2	53·9
1901-10												
Deaths	10,368	2,391	4,471	1,670	897	513	9,942	394	15	5	12	9,532
Rate	48·6	457·0	951·2	344·3	189·1	110·5	411·4	18·0	0·7	0·2	0·1	39·8
1911-20												
Deaths	8·074	1,758	3,418	1,349	684	409	7,618	427	12	5	12	7,399
Rate	41·7	386·2	798·0	318·4	164·6	97·5	355·6	20·1	0·6	0·3	0·1	30·8
1921-30												
Deaths	4,025	940	1,809	610	281	168	3,808	200	8	4	5	3,548
Rate	19·2	247·4	476·1	164·9	80·3	49·4	209·2	10·9	0·4	0·2	0·(	14·6
1931-32												
Deaths	525	106	251	83	22	24	486	33	3	1		412
Rate	12·8	169·6	412·7	141·4	37·6	40·7	162·3	10·0	0·9	0·3	0·.	8·8
1933-34												
Deaths	517	80	244	78	48	25	475	36	3	—	3	439
Rate	13·0	136·2	418·1	137·5	85·1	44·5	165·8	11·2	1·0	—	0·1	9·6
1935-36												
Deaths	331	77	134	49	27	24	311	18	—	—	2	272
Rate	8·5	133·3	240·2	94·3	51·2	44·8	114·4	6·0		—	0·1	6·1

race, born and bred in the same country and at the same time. The germ of measles which attacks them is the same, bred at the same time and under the same climate. The difference between the herds is one of housing, nutrition, segregation, and the mobility of the individuals composing them.

These environmental factors, together with those just referred to, namely, the character and size of the susceptible herd as opposed to the character and size of the immunes, that is, whether immunity is permanent or transient, must govern the periodicity of the epidemic outbreak.

In New York the periodicity curve of measles appears at the present time to be

undergoing a state of evolution similar to that experienced by London in the period 1912–1918. Instead of an epidemic year being regularly followed by one of non-epidemicity, we observe here a phenomenon of " break step ". That is, we observe two successive years of epidemicity followed by one of non-epidemicity, and these are followed by the usual rule of an epidemic year being followed by a non-epidemic one, and then the curve repeats itself by a succession of two epidemic years followed by one of non-epidemicity. What is responsible for this " break-step " phenomenon as well as the persistent lower mortality of measles in New York when compared with that in London can as yet not be explained.

IN TEN-YEAR PERIODS (1851-1930), AND FOR THE YEARS 1931-1932, 1933-1934, AND 1935-1936

Females

All ages	0 –	1 –	2 –	3 –	4 –	0–5	5 –	10 –	15 –	20 +	Period
											1851-60
6,790	1,022	2,440	1,559	793	434	6,248	454	34	14	40	Deaths
49·3–	267·3	754·7	477·0	254·7	145·2–	380·4	33·2	2·8	1·1	0·5	Rate
											1861-70
8,486	1,456	3,249	1,850	945	488	7,988	397	41	15	45	Deaths
52·6	320·2	843·6	476·6	251·5	135·1	406·5	24·2	2·8	1·0	0·5	Rate
											1871-80
8,682	1,735	3,364	1,638	909	430	8,076	518	32	12	44	Deaths
46·3	332·3	736·4	360·9	206·1	100·8–	351·1	26·7	1·9	0·7	0·4	Rate
											1881-90
12,330	2,251	4,684	2,365	1,340	746	11,386	841	37	13	53	Deaths
58·2	406·9–	948·3	473·1	274·8	159·0	454·8	38·2	1·9	0·6	0·4	Rate
											1891-1900
12,484	2,490	5,066	2,190	1,276	699	11,721	682	25	8	48	Deaths
53·9	451·3	1,032·5	435·4	256·7	146·8	465·3	30·0	1·2	0·4	0·3	Rate
											1901-10
9,532	1,970	4,006	1,725	823	511	9,035	437	15	3	42	Deaths
39·8	381·1	856·0	358·3	171·8–	110·5	375·3	19·8	0·7	0·1	0·3	Rate
											1911-20
7,399	1,389	3,074	1,325	675	374	6,837	491	19	15	37	Deaths
30·8	310·6	724·1	315·7	163·9	90·0	322·7	23·1	0·9	0·7	0·2	Rate
											1921-30
3,548	694	1,599	610	274	144	3,321	194	8	3	22	Deaths
14·6	187·6	432·2	169·4	78·3	42·4	185·5	10·7	0·4	0·1	0·1	Rate
											1931-32
412	75	179	69	39	22	384	23	3	—	2	Deaths
8·8	122·2	301·2	119·9	67·8	37·3	130·2	7·1	0·9	—	0·1	Rate
											1933-34
439	84	178	67	36	31	396	38	—	—	5	Deaths
9·6	146·0	314·6	120·5	64·8	55·4	140·8	12·1	—	—	0·2	Rate
											1935-36
272	59	119	39	12	16	245	21	1	2	3	Deaths
6·1	104·9	224·3	77·4	23·3	30·3	92·8	7·2	0·3	0·5	0·1	Rate

The tables and charts are appended to illustrate various points which I have dealt with in this paper.

Table I provides a complete statistical analysis of the deaths and death-rates of measles for both sexes and for the different age-periods since 1851. It will be noted that : (1) Measles is more fatal amongst males at all times and at all ages. (2) There has been a steady decline in the measles death-rates and that this has been particularly evident since 1921. (3) In London measles is most fatal at the age-periods 1 and 2—more correctly 9 months to 2½ years. After 2½ years it becomes less serious and is of no importance after the 5th year of life.

Table II sets out the death-rates for measles, irrespective of sex, for the decennial periods 1861–1930.

TABLE II.—MEASLES.

Death-rates per 100,000 living at each age-period.

Period	All ages	0 –	1 –	2 –	3 –	4 –	5 –	10 –	15 –	20 +
1861-70 ...	57·2	348	869	485	247	128	24	2	1	0
1871-80 ...	50·8	365	771	364	199	104	26	2	1	0
1881-90 ...	63·4	454	991	476	273	162	37	2	1	0
1891-1900 ...	58·3	494	1,069	436	255	146	27	1	0	0
1901-10 ...	43·9	419	904	351	180	111	19	1	0	0
1911-20 ...	34·3	341	752	299	156	93	22	1	0	0
1921-30 ...	16·7	218	454	167	79	46	11	0	0	0

Table III shows the total deaths and death-rate of measles for the calendar years 1910–1937 in London and in New York.

TABLE III.—MEASLES 1910-1937.

	Comparative figures for London		Comparative figures for New York	
Year	Deaths (calendar year)	Death-rate (per 1,000)	Deaths (calendar year)	Death-rate (per 1,000)
1910 ...	1,986	0·44	785	0·16
1911 ...	2,577	0·57	659	0·14
1912 ...	1,828	0·40	671	0·14
1913 ...	1,547	0·34	628	0·12
1914 ...	1,376	0·31	560	0·11
1915 ...	2,286	0·51	630	0·12
1916 ...	822	0·19	490	0·09
1917 ...	2,019	0·50	560	0·10
1918 ...	1,649	0·42	790	0·14
1919 ...	353	0·08	218	0·04
1920 ...	1,016	0·22	736	0·13
1921 ...	244	0·05	165	0·03
1922 ...	1,563	0·34	977	0·17
1923 ...	386	0·08	245	0·04
1924 ...	1,330	0·29	506	0·09
1925 ...	345	0·07	130	0·02
1926 ...	933	0·20	706	0·12
1927 ...	181	0·04	37	0·01
1928 ...	1,318	0·30	346	0·06
1929 ...	206	0·05	29	0·00
1930 ...	1,027	0·23	154	0·02
1931 ...	115	0·03	134	0·02
1932 ...	822	0·19	58	0·01
1933 ...	101	0·02	213	0·03
1934 ...	855	0·20	25	0·00
1935 ...	19	0·00	105	0·01
1936 ...	584	0·14	81	0·01
1937 ...	25 (52 weeks)	0·01	25	0·00

It will be noted that throughout these years both the total deaths and the death-rates are lower in New York than they are in London.

It may be asked, why is there this difference ? It is not due to season, for measles in both cities occurs at the same time of year. It is not due to such a fatal complication as bronchopneumonia being excluded from the measles deaths, for if we examine the bronchopneumonia deaths in London and New York we find the number in London three to four times as great as in New York (*see* Table IV). It should also be remembered that pneumonia is a more serious and fatal disease in New York than in London. A possible cause of the better positioning of measles in New York may be found in the fact that the New Yorker, however poor, has a better appreciation of the value of preventive measures than the Londoner. For instance, the teeth of a New York child are better cared for than those of the London child. The New Yorker has a better appreciation of the value of diet. Preventive measures may possibly be found to be the cause.

TABLE IV.—LONDON.

Deaths from measles and pneumonia.

Age-period	Measles deaths 1923	1924	1925	1926	1927	Total	Bronchopneumonia deaths 1923	1924	1925	1926	1927	Total	Pneumonia (all forms) 1923-1927
0-1	88	287	72	227	46	720	705	1,028	875	742	737	4,087	4,713
Births	..	...	...	...	...	411,298	...	...	...	...	...	411,298	
D.R. per 100,000 births	...	...	...	...	...	175·1	...	...	...	...	...	993·7	1,145·9
1-5	286	969	249	659	124	2,287	468	948	608	597	613	3,234	4,008
Population	...	...	...	...	...	246,197	...	...	...	...	...	246,197	
D.R. per 100,000 living	...	...	..	...	...	185·8	...	...	...	...	...	262·7	325·6
5-10	11	56	22	40	8	137	34	34	47	29	53	197	368
Population	...	...	...	...	...	342,843	...	...	...	...	...	342,843	
D.R. per 100,000 living	...	...	...	...	...	8·0	...	...	...	...	...	11·5	21·5
10-15	—	7	—	—	—	7	8	9	13	7	12	49	157
Population	...	...	...	...	...	337,753	...	...	...	...	...	337,753	
D.R. per 100,000 living	...	...	...	...	...	0·4	...	...	...	...	...	2·9	9·3
15+	1	18	2	7	3	31	1,002	1,107	1,236	1,157	1,160	5,662	
D.R. per 100,000 living	...	...	...	..	...	0·2	...	...	...	...	...	28·7	

NEW YORK CITY.

	Measles	Pneumonia (all forms)
0-1 D.R. per 100,000 births	66·7	1,373·9
1-5 D.R. per 100,000 living	45·7	249·8
5-10 D.R. per 100,000 living	3·7	28·7
10-15 D.R. per 100,000 living		17·8
10+ D.R. per 100,000 living	0·1	

TABLE V.—EFFECT OF LATITUDE ON MEASLES MORTALITY 1922-1930.

Mortality per 100,000 *Living at Ages* 0-5 *in England and Wales.*

	1922	1923	1924	1925	1926	1927	1928	1929	1930	Average
NORTH.										
County Boroughs ...	264	209	205	241	132	232	130	229	160	200
Other Urban Districts	153	188	120	184	72	153	60	104	103	126
Rural Districts ...	87	156	34	153	36	113	47	104	59	88
All Areas	203	195	154	210	99	190	96	172	128	161
MIDLANDS.										
County Boroughs ...	162	157	106	198	78	111	106	143	105	130
Other Urban Districts	70	113	81	84	71	32	101	30	100	76
Rural Districts ...	28	63	29	44	38	26	38	28	37	37
All Areas	90	115	76	112	64	57	86	68	86	84
SOUTH.										
London	375	89	285	77	219	44	346	56	287	198
County Boroughs ...	92	101	45	64	58	96	142	17	186	89
Other Urban Districts	56	54	66	35	76	12	81	27	67	53
Rural Districts ...	23	26	31	20	29	21	56	15	34	28
All Areas	198	71	157	55	130	39	201	36	170	117
WALES.										
County Boroughs ...	70	240	71	260	31	128	64	292	112	141
Other Urban Districts	59	259	24	259	40	87	109	93	74	112
Rural Districts ...	36	82	21	69	38	62	55	24	36	47
All Areas	54	204	33	205	38	88	83	115	71	99
ENGLAND AND WALES.										
London	375	89	285	77	219	44	346	56	287	198
County Boroughs ...	206	184	152	211	103	175	121	183	143	164
Other Urban Districts	94	145	85	129	68	75	85	60	92	93
Rural Districts ...	42	78	30	66	35	50	46	43	42	48
All Areas	154	138	120	138	91	101	119	99	121	120

1922-1930.

	North	Midlands	South	Wales	England and Wales
London	—	—	198	—	198
County Boroughs ...	200	130	89	141	164
Other Urban Districts ...	126	76	53	112	93
Rural Districts	88	37	28	47	48
All Areas	161	84	117	99	120

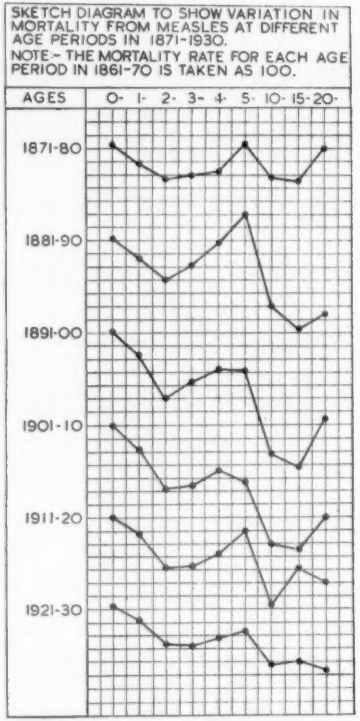

CHART I.—Measles mortality curve for the different ages (0-20 years) in London from 1871 to 1930 in ten-year periods.

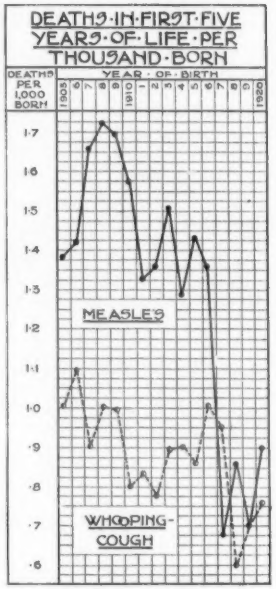

CHART II.—Measles mortality curve in the first five years of life per 1,000 born.

It will be noted that there has been a material improvement in the measles mortality of babies born since the year 1916.

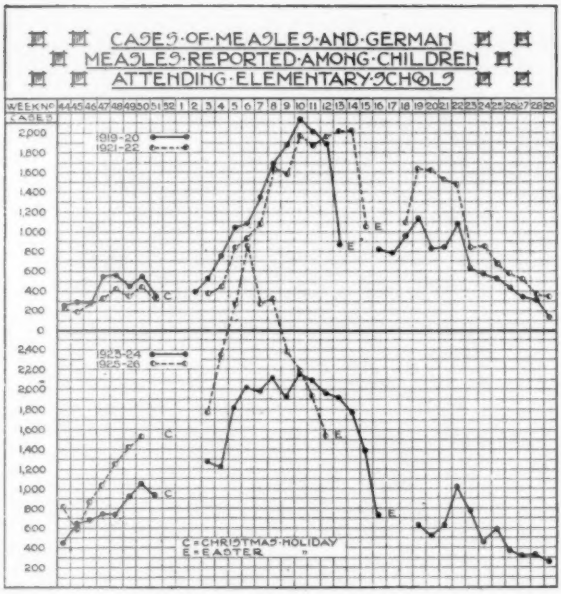

CHART III.—Measles cases reported from elementary schools in London during an epidemic period.

It will be noted that the increased prevalence of measles begins to show itself about the first week in November. The Christmas holiday usually causes a slacking-off, and it is not until three or four weeks after the schools reopen that the cases substantially increase. Thereafter the number of cases increases rapidly to a maximum which is reached in March or April. Then there is a rapid drop and the epidemic exhausts itself by the end of May.

Mortality of measles is closely associated with incidence, the greatest fatality occurring a week or two after the greatest incidence. When a school is attacked it is usually found that the epidemic exhausts itself in that school in about four weeks.

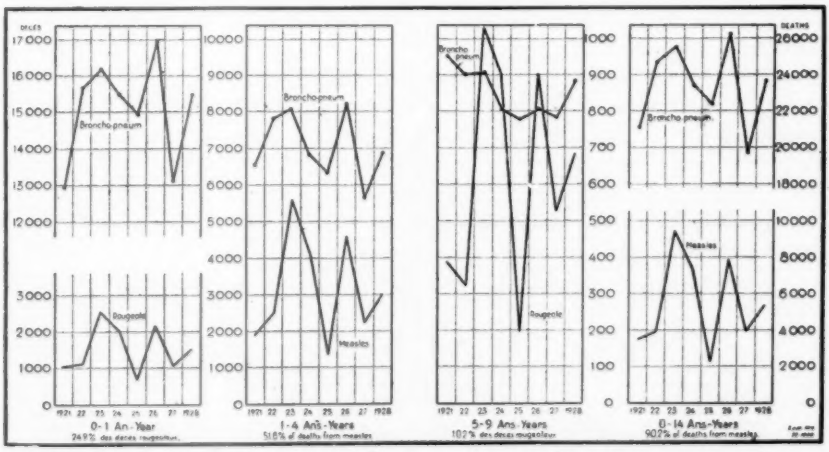

CHART IV.—Co-variation between mortality from measles and from bronchopneumonia from 0-14 years, from 1921-1928 in the United States of America. (Absolute figures for deaths.)

It will be seen that the mortality of measles follows that of pneumonia and does not anticipate it. Bronchopneumonia following on an attack of measles is therefore one of the telling factors in the mortality of measles.

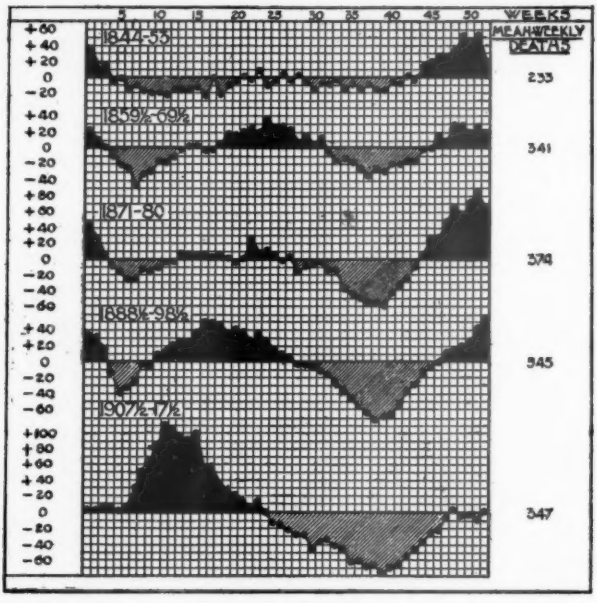

CHART V.—Measles : mean weekly deaths in ten-year periods. Illustrating Sir W. Hamer's criticism of Brownlee's contention (*see* p. 44).

To make the argument clearer, the chart is calculated on a mean mortality for ten-year periods. Note that in the decennial period 1859–1869 the maximum measles mortality was in mid-summer. In subsequent decennial periods the maximum has gradually shifted until in the decennium 1907–1917 the maximum mortality was in the spring, and this has remained so ever since.

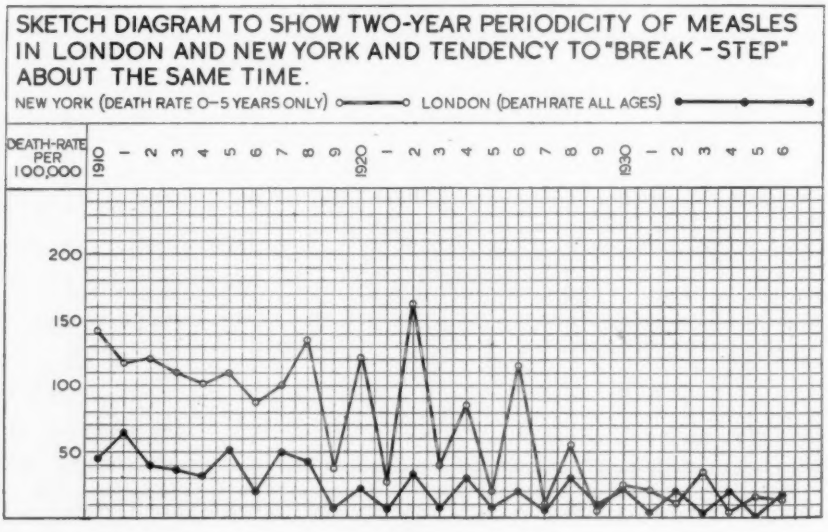

CHART VI.

Note the " break-step " phenomenon which has occurred in New York recently. This break-step phenomenon, the cause of which is as yet undetermined, also occurred in London in 1907–1908.

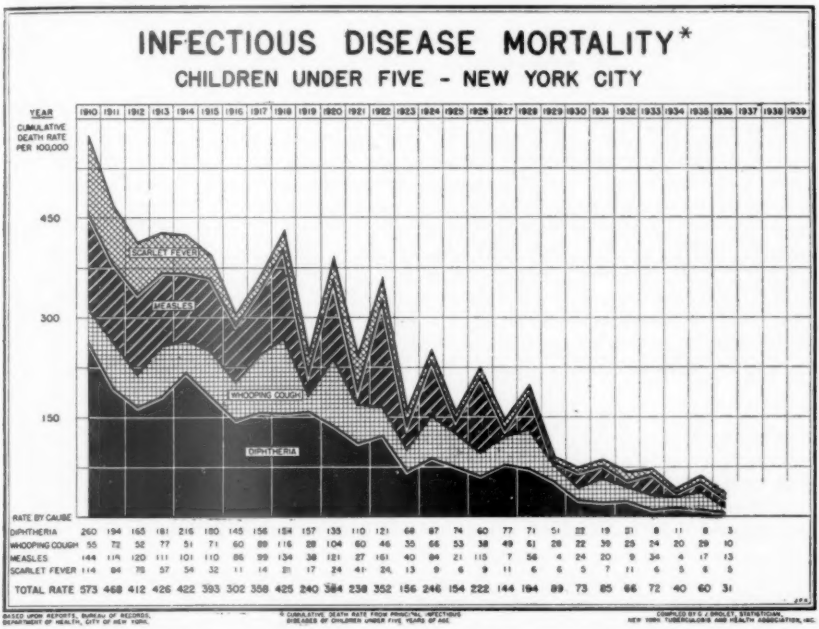

CHART VII.—Showing the incidence of the more common infectious diseases in New York.

It will be noted that measles is the outstanding feature that regulates the curve. The " break-step " phenomenon is also to be observed here.

[I am deeply indebted to Mr. W. L. Parry of the Public Health Department, and to Mr. B. E. Spear of the Statistical Section of the Public Health Department, London County Council, both for the material contained in these tables and charts and for advice given during the writing of this paper.]

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The Serum Prophylaxis of Measles

By William Gunn, M.R.C.P., D.P.H.

I intend in this paper to restrict myself to the clinical aspects of the subject with which I am more directly concerned. If I appear unduly obsessed by the shortcomings of the serum prophylaxis of measles I plead in extenuation that the great success of the earlier experiments has intensified recent disappointment over results which have proved to fall somewhat short of that measure of success.

The use of immune serum in measles prophylaxis was first suggested by the laboratory researches of Anderson and Goldberger. These workers in 1911 inoculated monkeys with material derived from acute cases of measles, and obtained febrile reactions, with or without rashes, in about one half the inoculated animals; they found successful reinfection to be impossible, presumably on account of the presence of antibodies in their blood following the primary inoculation. The credit for the first employment of immune serum in measles prophylaxis is usually attributed to Nicolle and Conseil who applied the method in 1916 in Tunis but did not publish their results until 1918. Zingher, in collaboration with Park, carried out preliminary experiments in the same year (1916), but details of their inoculations were withheld until 1924 (Zingher). In their hands the measure gave highly satisfactory results and was thereafter widely practised with a high degree of success in America and on the Continent, particularly by Degkwitz in Munich and Debré in Paris. We in this country were slow to take notice of the new method.

In 1925 Dr. W. S. C. Copeman made us familiar with the technique of measles control by means of serum, and two years later Miller and Smith gave an account of 10 cases which they had treated in private practice at Harrogate. Five of the 10 inoculated were apparently protected, and the remaining five had clearly modified attacks. Later in the same year, Benson and Lawrie described an account of a ward outbreak of measles successfully controlled by serum in the Edinburgh City Fever Hospital, and Kingsbury (1927) described an extensive experience of the method among natives on Malayan rubber estates. McClean in 1928, in a brief note on the use of immune serum in three cases, expressed disappointment with his results; his failures were probably due to the fact that the serum he used was not pooled from several donors. Towards the end of 1927 the method was first applied in one of the fever hospitals under the control of the late Metropolitan Asylums Board, and the results were published at the end of 1928. In the preliminary experiments convalescent serum was compared side by side with Tunnicliff's measles antitoxin (horse), Ferry and Fisher's measles antitoxin (horse), and Degkwitz's immune serum (sheep). It was found possible to arrive at a decisive verdict on the merits of these reagents;

in brief, that convalescent serum alone was consistently effective as a measles preventative; the others were either inert or uncertain in their action. As a result, all efforts have ever since been devoted to increasing the quantity and availability of serum supplies. From 1928 to 1930 the method was increasingly used in the London fever hospitals, but it was not until after 1930, when the London County Council took over these hospitals, that serum production on a large scale was begun. From the first, the task of preparing serum in a form suitable for general issue was undertaken by Dr. McCartney, Director of the Southern Group Laboratories at the Park Hospital, without whose willing co-operation and genius for organization large-scale production and distribution of the product would not have been possible. The task of preparing serum for general use is one which few bacteriologists are willing to undertake, especially in a laboratory where routine and research are carried on at the same time. The best tribute to Dr. McCartney's work is the fact that no instance of sepsis or untoward effect, or of loss of serum potency due to faulty preparation, has come to our notice during these ten years in which upwards of 10,000 inoculations have been given.

But serum manufactured by one authority for its own domestic use is unlikely to be of much interest to the majority of medical practitioners who are unable to get the material or to have an opportunity of becoming familiar with the technique of using it. The pioneer work of Nabarro, working in collaboration with Massingham of the London Fever Hospital, admirably filled the gap for two or three years until local authorities were in a position to secure stocks for themselves or commercial firms were able to manufacture serum. At the present time stocks of varying amounts, chiefly of adult serum, are held by the public health authorities of the principal cities and towns of this country; the majority have found it convenient to seek the aid of a laboratory specially equipped for this type of work.

Following the work of McKhann and his colleagues in America in 1933, placental extracts were prepared in 1935 at the Lister Institute Laboratories, Elstree, and shortly afterwards in the London County Council serum establishment at Sutton. The London County Council holds a large stock of measles serum—at present about 60 litres—of which the great bulk is adult serum; this authority does not sell the substance but makes it available to medical officers of health or to private doctors through their local medical officers of health. For urgent cases, in which protection is deemed to be imperative, the more valuable convalescent serum has occasionally been provided through the same channel.

Despite these facilities it is clear that there is a great need of some centralized organization whereby all serum supplies are pooled—particularly convalescent serum, which is usually not available at the beginning of an epidemic when it is most needed, but may be available in large quantities at its termination when the need for it tends to reach vanishing point. Moreover, in the interval between the end of one epidemic and the beginning of another—on an average a period of fifteen months—serum tends to deteriorate, even though stored under the best conditions. By the end of one year it has been calculated to have lost 25% of its potency, and by eighteen months about 50%. To obviate this loss we had about 2 litres of convalescent serum dried in 1933 (the last ½ litre of this dried serum was exhibited in a glass container). At that time serum could not be dried in bulk in this country, and this serum was accordingly sent to Munich, where desiccation was carried out. The substance has been tested at intervals by reconstituting the powder in saline according to the formula received from the makers: so far its potency appears to have remained unimpaired. Last year Dr. McCartney acquired a plant for the drying of serum on a large scale, since which time over 30 litres of adult serum have been so treated (1 litre of serum dried recently at the Southern Group Laboratory was shown).

I am not going to describe in detail the method of preparation of the different materials, since this belongs to the province of the serologist, but a word in passing about placental extract may not be out of place, as this substance is not yet generally

known in this country. Almost from the first, encouraging reports of its use were published by McKhann and his co-workers in America ; it was held to be only slightly less potent than convalescent serum and the latest reports appeared to indicate that oral, or combined oral and parenteral, administration of these extracts is even more efficacious than convalescent serum. Severe reactions following inoculation, common at first, were later largely avoided by improved methods of preparation and by reduction of the volume in each dose. Personal experiments with placental extracts have proved far from encouraging ; the protective value of these extracts did not appear to be any greater than that of adult serum, and the local and constitutional reactions which not infrequently followed were a serious disadvantage. Before undertaking the preparation of placental extracts Dr. White, of the L.C.C. Laboratories at Belmont, carried out preliminary experiments on the fractional analysis of adult measles serum into the protein constituents—albumin, euglobulin, and pseudoglobulin. Albumin was found to be practically inert in measles prevention while the two globulins approximated in potency, the advantage usually lying with euglobulin. Similar protein fractions were later prepared from placental tissues and comparative tests of these substances gave practically the same results. Neither of the placental globulins showed itself on clinical test to be much superior to adult serum. As the method of preparation might conceivably have been faulty, 100 doses of placental extract of American manufacture were obtained for trial ; the dose of 2 c.c. recommended by the makers was soon found to be inadequate and even three or four times that amount sometimes failed to produce the effects claimed. In short, on clinical trial these extracts were found to be hardly more potent than the later products of the Lister Institute and Belmont serum establishments. The conclusion arrived at was that the comparative potencies of convalescent serum, placental extract (the best samples) and adult serum, volume for volume, were approximately of the order of 1, 0·75, and 0·5. Further experiments with placental extracts are being continued, but unless they are found to give better results than in the past their preparation will be abandoned. Extraction of placental globulins is a difficult and tedious process : in the various manipulations the risk of accidental contamination of the product is much greater than in the preparation of convalescent or adult serum.

Despite the utmost care in the preparation of serum and in the selection of suitable donors, it may be difficult to ensure that the substance is not contaminated by some poison or living agent, the introduction of which into a recipient might lead to serious consequences. While filtration and the addition of antiseptic are found to be adequate safeguards against bacterial contamination they cannot with certainty exclude the entry of filtrable viruses. To lessen this particular risk donors are usually kept under supervision for three weeks after bleeding, in order to eliminate any risk that they were incubating an infectious disease due to a filter-passing agent. It is now the practice in the London County Council to follow up all recipients for a period of three months after inoculation in order to ascertain if untoward effects have ensued. As far as is known, no such effects have so far followed inoculations in their extensive series of cases.

The expected demand for immune serum is necessarily related directly to the prevalence of measles. As Dr. Brincker has pointed out, measles epidemics visit London with more or less regularity every second year ; at this moment we are meeting the vanguard of the 1937–38 epidemic. Ever since 1924, when the late Metropolitan Asylums Board decided to admit measles cases as far as accommodation permitted, each successive epidemic in London has witnessed an increase in the numbers admitted to fever hospitals for treatment. Fig. 1, which shows the yearly number so admitted since 1924, illustrates well the biennial periodicity of the disease, but its explosive character is obscured by the fact that annual figures of admission are given, not the figures relating to each epidemic. It is unlikely that the magnitude of measles epidemics has altered much in the last decade, but a larger proportion of

measles cases are undoubtedly being admitted to hospital. Whether the results of hospitalization are commensurate with the expense involved is outside the scope of the present discussion; there can be no doubt that mortality has been greatly

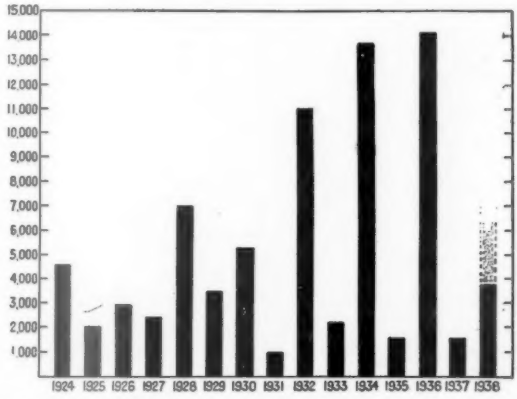

FIG. 1.—Annual measles admissions to London Fever Hospitals (M.A.B. and L.C.C.), 1924-1938.

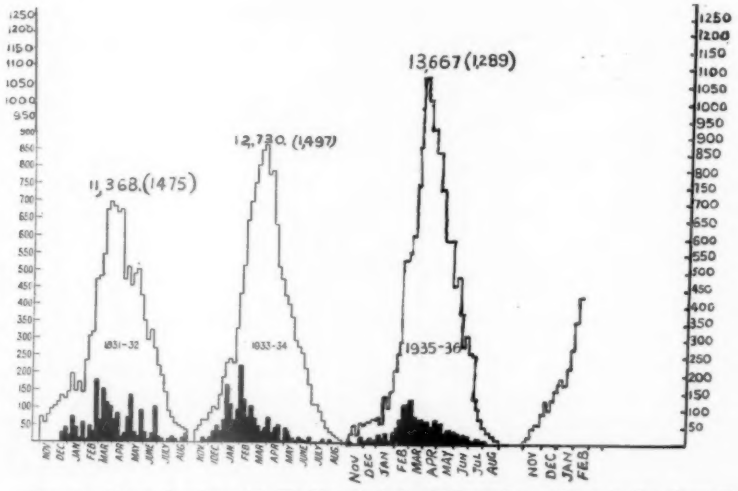

FIG. 2.—Chart showing: (*a*) Weekly admissions of measles patients to the Council's fever hospitals (plain area). (*b*) Weekly inoculations of adult measles serum in all the Council's institutions (shaded), for the periods November 1, 1931 to August 31, 1932; November 1, 1933 to August 31, 1934, and November 1, 1935 to August 31, 1936.

reduced, but in all probability a considerable proportion of those admitted would have recovered equally well if nursed at home.

Fig. 2 shows more clearly the explosive character of measles epidemics in London. The weekly number of inoculations of adult measles serum is given for the same

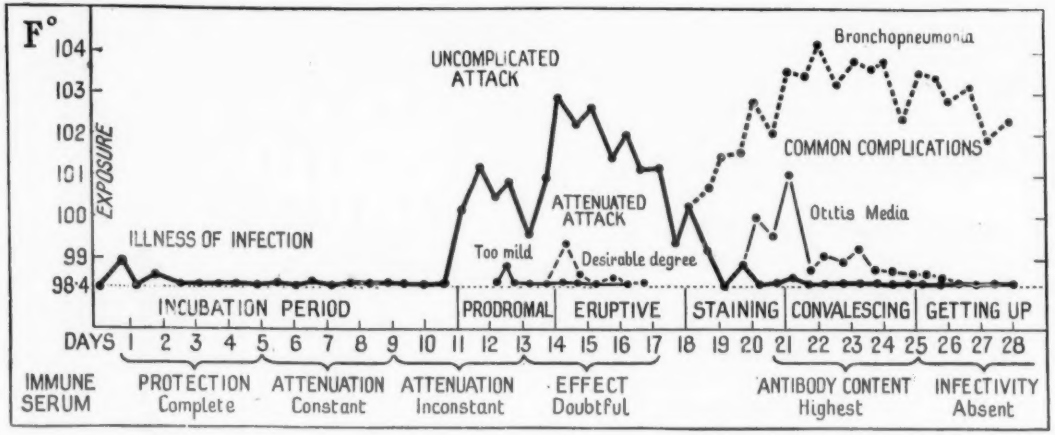

FIG. 3.—Synoptic chart showing the typical course of measles: (1) Uncomplicated; (2) with the two commonest complications; (3) attenuated by immune sera (*a*) to the desirable degree and (*b*) to an undesirable degree with an attack too mild to confer lasting immunity.

The dosage, route and time of administration of the different measles immune agents for (*a*) protection (*b*) attenuation, are as follows:—

Serum	Minimum dose	Dosage factor	Route	Time
Convalescent	5 c.c. ...	Age × 2	Intramuscular	1st to 6th day
Normal adult	10 c.c. ...	Age × 4	,,	,,
Whole blood double the homologous serum		Age × 4	,,	,,
Placental extract ...	7·5 c.c. ...	Age × 3	,,	,,

For attenuation, administration on the 6th to 9th day after exposure or one-half of the above doses in the first six days.

periods. It is seen that serum is always used more frequently in the earlier stages of epidemics, but there are often irregular fluctuations in the demand. Adult serum was used less and less during each successive epidemic, the ratio of inoculations to admitted cases being 1 : 7·7 in 1931–32 ; 1 : 8·5 in 1933–34 ; and 1 : 10·6 in 1935–36. This does not necessarily mean that there was any relaxation in the endeavour to prevent or seek attenuation of measles, but that opportunities for administering it became fewer. As more isolation accommodation was made available, outbreaks of measles in hospital wards were reduced in number and magnitude. The progressive reduction in the use of convalescent serum is even more striking, the ratio to admissions being 1 : 29 in 1931–32 ; 1 : 35·4 in 1933–34 ; and 1 : 112 in 1935–36.

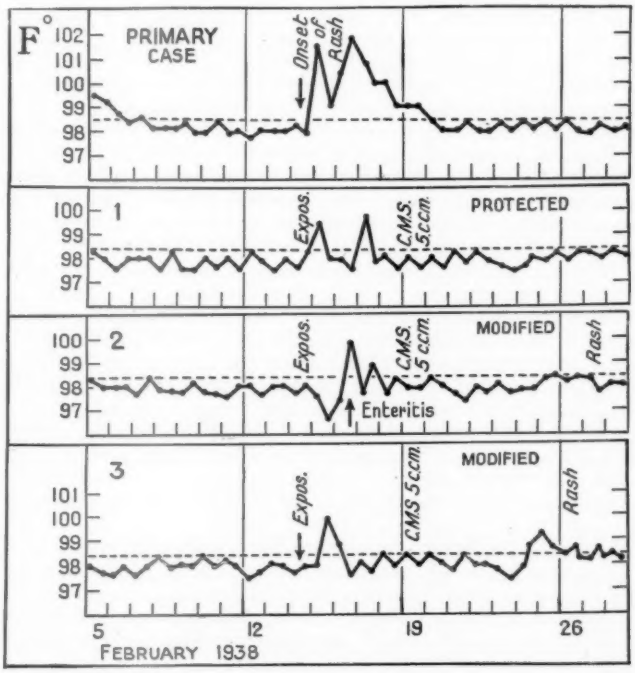

FIG. 4.—Introduction of measles into whooping-cough ward; among 16 non-immune contacts three showed the "illness of infection". One of the inoculated was apparently protected by serum, while the remaining two had markedly modified attacks, showing less fever and constitutional disturbance than the illness of infection. Expos. = date of exposure to infection. C.M.S. = convalescent measles serum.

(Figs. 1, 3 and 4 are reproduced by kind permission of the *Lancet*.)

Before proceeding to a consideration of the results of serum prophylaxis during the last three London epidemics, I wish to mention briefly the doses of the different kinds of prophylactic which are generally employed, and the conditions of inoculation which must be observed to ensure a reasonable likelihood of success (fig. 3).

The first essential is to ascertain whether a given individual has been effectively exposed to infection. Unfortunately we have no certain guide to this although

three different signs have been described. The "illness of infection" described by Goodall in 1925 has been observed by a number of workers, but uncertainty still remains whether the phenomenon is a specific reaction of the order of an abortive measles attack or is merely a mild coryza. Moreover, it occurs too infrequently to be of practical value in the majority of outbreaks. Fig. 4 (p. 59) shows the temperature charts of four patients at present in the North Western Hospital. On February 14 one of the patients in a whooping-cough ward developed measles ten days after admission; three of the 19 patients thereby exposed showed febrile reactions with slight pyrexia, coryza, and, in one instance, enteritis. They each received 7·5 c.c. of immune serum, that is, an increase of 50% on the usual dose, as there was reason to believe that deterioration of serum had occurred owing to the fact that it was nearly two years old. This suspicion was amply confirmed. Two of the three inoculated contacts developed a markedly attenuated attack as seen by a discrete morbilliform rash, unaccompanied by symptoms, on the fifteenth day after exposure, while the third escaped. Five others who did not have the illness of infection had similarly modified attacks. Another phenomenon occurring in the incubation period, loss of weight from the fourth to the eighth day after exposure, first described by Meunier in 1898, is also too uncertain to deserve much reliance; it is probably due, as Teissier suggested, to environmental and dietetic changes incidental to isolation of contacts rather than to the specific effects of invasion by measles. Nor are the blood changes described in the incubatory period sufficiently pronounced or constant to warrant a decision as to whether the patient has been infected; leucocytosis affecting principally the neutrophils—changing to leucopenia shortly before the appearance of the rash—is the usual finding, but the changes may appear too late for serum to be employed, at least for protection; or, on the other hand, if serum has already been given it may prevent the appearance of the changes in the blood.

Unfortunately there is no laboratory method of testing the potency of serum, and it may happen that the inferiority of a weak sample is not known until it has been all injected. The rash-inhibition phenomenon described by Debré may serve as a rough guide of serum potency, but opportunities of applying it are infrequent, in view of the fact that prevention rather than attenuation is mainly sought in outbreaks in hospital wards and similar semi-closed communities. A serious disadvantage of the increased use of serum is that control experiments tend to become fewer, as it is felt that every known contact should receive the benefit of serum prophylaxis either in prevention or attenuation.

Before passing on to a detailed consideration of the results of the use of convalescent and adult serum and placental extracts in the 1935–36 measles epidemic in London, I wish to draw attention to the comparative results of these two sera in the last three epidemics. While these remain fairly constant for adult serum they appear to be less favourable for convalescent serum in each successive epidemic period.

TABLE I.—COMPARISON OF RESULTS OF CONVALESCENT AND ADULT SERUM DURING THE EPIDEMIC PERIODS, 1931-32, 1933-34, AND 1935-36.

A.—Protection desired	% protected		
	1931-32	1933-34	1935-36
Convalescent serum ...	90·7	80·8	72·3
Adult serum	78·6	78·3	72·4

B.—Attenuation desired	% attenuated		
	1931-32	1933-34	1935-36
Convalescent serum ...	No obs.	54·3	20·0
Adult serum	37·4	38·5	31·5

The explanation is probably to be found in the fact that as the range of these investigations is increased there is a corresponding lowering of accuracy in observing

the requisite conditions. Possibly the fault lies chiefly in lack of care in the selection of donors, e.g. using German measles convalescents instead of measles cases.

TABLE II.—RESULTS OF PROTECTION EXPERIMENTS WITH CONVALESCENT SERUM, ADULT SERUM, AND PLACENTAL EXTRACTS AMONGST CHILDREN 0-10 YEARS DURING THE EPIDEMIC PERIOD, 1935-36.

Serum	Number of children observed	Results %					
		Protected		Attenuated		Unmodified	
Convalescent	109	71·6		25·7		2·7	
Adult	1,033	72·1		17·3		10·6	
,, (pseudoglobulin) ...	9	100·0	77·3	—	13·6	—	9·1
,, (euglobulin)	13	61·5		23·1		15·4	
P.E. (Lister)	20	60·0		25·0		15·0	
,, (L.C.C. euglobulin) ...	12	75·0		16·7		8·3	
,, (L.C.C. pseudoglobulin)	4	—	67·8	50·0	17·8	50·0	14·4
,, (Lederle)	14	—		50·0		50·0	
,, Type unknown ...	40						

In Table II the various immune substances used in the 1935–36 epidemic are compared directly with each other. Unfortunately, the number of observations in the different groups differ widely, but the convalescent and adult serum-employing series are sufficiently large to show that the results of each are practically identical—the appropriate dose of adult serum being twice that of convalescent serum—while placental extracts generally speaking give less favourable results; these are seen to vary considerably, particularly in respect of unmodified attacks. As age is an important factor in determining the issue, the inoculated subjects in each series were further classified according to specific age-groups.

TABLE III.—NUMBERS INJECTED (CLASSIFIED ACCORDING TO SPECIFIC AGE-GROUPS) WITH DIFFERENT KINDS OF IMMUNE SERUM DURING 1935-36 EPIDEMIC.

Age-group	Convalescent serum	Adult serum	Adult serum		Placental extract			Unknown
			euglobulin	pseudoglobulin	Lister	Lederle	Belmont	
0-6 months	2	130	1	1	3	1	—	4
6-12 ,,	21	171	1	2	—	1	2	7
1-3 years	52	556	8	3	16	7	9	12
3-5 ,,	30	256	3	3	4	7	10	9
5-10 ,,	14	152	1	—	3	2	12	6
10+ ,,	3	24	—	—	—	—	3	2
All ages	122	1,289	14	9	26	18	36	40

It is seen from the table that none of the substances enjoyed any particular advantage except adult serum in respect of the relatively large numbers belonging to the 0–6 months age-group, in which an appreciable number are likely to have retained partial or complete immunity from their mothers. A closer comparison between the protective values of convalescent and adult sera is effected in Table IV in which the percentage of protections obtained when sought (i.e. true successes) are detailed in each age-group.

TABLE IV.—COMPARISON OF CONVALESCENT AND ADULT SERUMS ACCORDING TO AGE-PERIODS, IN 1935-36 EPIDEMIC. (AIM = PROTECTION.)

Age-group	Convalescent serum		Adult serum	
	Observed	% Protected	Observed	% Protected
0-6 months	2	100·0	123	92·7
6-12 ,,	19	78·9	150	74·7
1-3 years	50	70·0	456	63·6
3-5 ,,	27	63·0	194	73·7
5-10 ,,	11	81·8	110	78·2
10+	3	100·0	22	86·4
All ages	112	72·3	1055	72·4

It is noteworthy that the protection rate for both sera is highest at the same age-periods, 0–6 months and 10+ years, when natural immunity is probably high. The results are least favourable with both sera at ages 1–5 years : for convalescent in the 3–5 years group and for adult serum in the 1–3 years group. Despite these minor differences a striking parallelism is seen between the two series suggesting that the results may actually flatter both. An alternative explanation of the divergencies of the efficiency of the sera at different ages is improper adjustment of dosage to age or body-weight. The general indication emerging from these findings is that the dosage should be increased all round, particularly in the 1–5 years group.

It is pertinent to inquire into the possible bearing of other factors, some of which may be more or less under our control. For instance it has been considered that the sooner after exposure immune serum is administered the more probable is complete protection to ensue. This particular point is examined in Table V in which the results of injection are compared according to the reagent given (*a*) in the first three days after exposure, (*b*) between the third and sixth days, and (*c*) after the sixth day.

TABLE V.—THE EFFECT OF THE INTERVAL BETWEEN EXPOSURE AND INJECTION ON THE RESULTS DURING THE MEASLES EPIDEMIC 1935-36.

	Convalescent serum								Adult serum							
	Protection				Attenuation				Protection				Attenuation			
		Result %				Result %				Result %				Result %		
Interval	Observed	P.	A.	U.	Observed	P.	A.	U.	Observed	P.	A.	U.	Observed	P.	A.	U.
1-3 days	58	63·8	31·2	5·2	3	100·0	—	—	609	71·1	18·7	10	58	50	39	10
3-6 ,,	41	75·6	24·4	—	6	66·7	33	—	354	75·4	15·0	9	111	55	25	19
6+ ,,	13	100·0	—	—	1	100·0	—	—	89	68·5	13·5	31	64	32	32	3

P, Protected. A, Attenuated. U, Unmodified.

Only the protection experiments with either serum are suitable for making a comparison of the effect of different exposure-injection intervals in influencing the results. In the convalescent serum series it appears that the results improved as the time of injection was postponed, although the number of observations of 6+ days' interval inoculations is too small for any conclusion to be drawn. In the adult serum series the 6+ days' interval cases show the least favourable results, while the three to six days' interval cases fared better than those inoculated before the third day ; this also was true for the convalescent serum cases. These findings are in sharp contradiction of the observations made during the two previous epidemics. The other important factor which may influence the issue is the duration of exposure of contacts to the primary infecting case ; this aspect of the problem is investigated in the following table.

TABLE VI.—THE BEARING OF THE DURATION OF EXPOSURE ON THE RESULTS OF SERUM ADMINISTRATION DURING THE 1935-36 EPIDEMIC.

	Convalescent serum						Adult serum					
	Protection Result %			Attenuation Result %			Protection Result %			Attenuation Result %		
Duration of exposure	P.	A.	U.	P.	A.	U.	P.	A.	U.	P.	A.	U.
1-3 days	64·7	29·4	5·9	100·0	—	—	73·1	15·3	11·6	45·9	33·7	20·4
3-6 ,,	79·6	20·4	—	80·0	20·0	—	72·6	18·6	8·8	56·2	34·2	9·6
6+ ,,	71·4	28·6	—	50·0	50·0	—	69·7	18·2	12·1	82·2	10·7	7·1

P, Protected. A, Attenuated. U, Unmodified.

The results of administration of serum to contacts who have been exposed to measles for varying intervals do not show differences sufficiently marked to be of statistical significance. Probably little difference is to be anticipated, as the primary

infecting cases are most infectious in the first three or four days of the illness; thereafter infectivity diminishes rapidly and is negligible by the sixth day.

The only control experiments available in recent years are those relating to cases in which serum has been given, either for prevention or attenuation, and in which attack of some sort has ensued; these may be compared directly in point of severity with the cases which infected them. These primary infecting cases, as they are usually termed, form an ideal control group, as by virtue of their intimate relation to the secondary cases, the possibility of varying virulence of different strains of the causative organisms is eliminated. A comparison based on complication and fatality rates is made in Table VII; Table VIIa, detailing the numbers in each age-group, is important in assessing the results, as an undue proportion of young individuals in a particular group might affect the results unfavourably. It is seen that any age bias

TABLE VII.—COMPARISON OF (*a*) CONTROLS (UNINJECTED), (*b*) ATTENUATED, AND (*c*) UNMODIFIED ATTACKS, AFTER SERUM ADMINISTRATION.

London County Council.—Measles.

	Observed	With complications	Deaths
Attenuated cases	273	25 (9·2)	1 (0·4)
Unmodified cases	144	55 (38·2)	9 (6·3)
Primary infecting cases	84	28 (33·3)	3 (3·6)
Controls other than primary ...	329	52 (15·8)	10 (3·0)

TABLE VIIa.—AGE DISTRIBUTION OF ABOVE CASES.

Age-group	Primary cases (controls)	Attenuated attacks	Unmodified attacks
0-½	—	7 (2·6)	3 (2·1)
½-1	5 (6·2)	24 (8·8)	23 (16·0)
1-3	41 (50·6)	133 (48·7)	88 (61·1)
3-5	20 (24·7)	79 (28·9)	19 (13·2)
5-10	14 (17·3)	27 (9·9)	9 (6·2)
10+	1 (1·2)	3 (1·1)	2 (1·4)
All ages	81 (100·0)	273 (100·0)	144 (100·0)

that exists favours the primary infecting group in which there were none under 6 months and only 6·2% under 1 year, while there were 8·8 and 16% of that age amongst the attenuated and unmodified groups, respectively. To the control series of primary infecting cases, 84 in number, may be added 329 cases, which were not infecting cases but developed measles in hospital not previously having received serum. The cases described as attenuated show clearly the favourable effects of serum in respect both of complication and fatality rates which are 9·2 and 0·4 respectively, against 33·3 and 3·6% for the primary infecting cases. On the other hand, the unmodified group fared worse than the primary cases; this may be attributed to two factors: (*a*) their average age was much lower than that of the primary cases, and (*b*) they were without exception suffering from an intercurrent disease often of considerable gravity, while the majority of the primary cases had measles only. The comparison is carried a stage further in fig. 5 (p. 64) in which the incidence of the chief initial manifestations and main clinical features of measles in each group are graphically presented; in every respect the results favour the inoculated cases, although in some the differences are too slight to be of statistical significance. It appears to be a fair inference from a study of these figures that the criteria adopted in assigning individual cases to the unmodified category were sometimes unduly stringent; a proportion might with justification have been placed in the attenuated group. The higher complication and fatality rates noted amongst the unmodified (injected) cases

may have been due, as previously suggested, to the influence of concurrent disease. This aspect of the problem is examined in Table VIII in which a direct comparison is

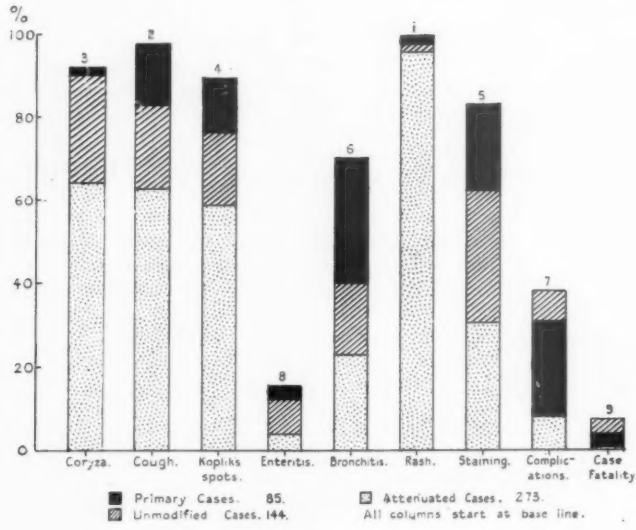

FIG. 5.

made between the results of serum attenuation amongst individuals suffering from concurrent scarlet fever, diphtheria, and whooping-cough, respectively.

TABLE VIII.—THE RELATION BETWEEN CONCURRENT DISEASE AND THE INCIDENCE OF COMPLICATIONS AND DEATHS AMONGST CHILDREN WHO DEVELOPED ATTENUATED OR UNMODIFIED ATTACKS OF MEASLES AFTER SERUM INJECTION

		Complications of Measles				
		Enteritis	Bronchopneumonia	Otitis	Other complications	Deaths
Concurrent disease	Observed	No. %	No. %	No. %	No. %	No. %
Scarlet fever ...	22	—	—	2 (9·1)	1 (4·5)	—
Diphtheria ...	8	—	—	—	—	—
Whooping-cough ...	93	1 (1·1)	8 (8·6)	1 (1·1)	4 (4·3)	5 (5·4)

Though the number of observations in each group vary considerably, it is clear that whooping-cough as a concurrent disease has a particularly unfavourable influence on measles prognosis; scarlet fever, as might be expected, led to a high incidence of otitis media, while all the diphtheria cases emerged from measles unscathed. It would appear desirable to seek protection, not attenuation, in the presence of coexisting whooping-cough and scarlet fever, while, in diphtheria, attenuation may be practised with safety.

As a measles epidemic advances to its termination it might be expected that protection rates would rise progressively, especially amongst closely commingled subjects in whom there is every likelihood of intimate contact. The protection and attenuation rates following administration of both adult and convalescent serum during the whole epidemic period in 1935–36 in London are given in the following table drawn up in order to test this hypothesis.

TABLE IX.

Period	Convalescent serum		Adult serum	
	Prevention desired			
	Observed	Protected	Observed	Protected
Aim—protection				
Dec. 1935 to Feb. 1936 ...	73	82·2	249	62·7
Mar. 1936 to May 1936 ...	26	30·8	643	70·9
June 1936 to Sept. 1936 ...	13	100·0	119	90·8
Total		72·3		72·4
Aim—attenuation		A.		A.
Dec. 1935 to Feb. 1936 ...	5	20·0	91	33·0
Mar. 1936 to May 1936 ...	5	20·0	98	30·6
June 1936 to Sept. 1936 ...			3	100·0
Total		20·0		31·5

The adult serum results support the hypothesis clearly, showing a definite trend towards improved protection rates in each successive quarter, but the poor results from convalescent serum in the March-May quarter have no satisfactory explanation. It is quite possible in a small series of observations (26), that one batch of low-titre serum might seriously disturb the results; in any event these findings should be regarded with reserve until a larger series or a more satisfactory explanation is forthcoming. Similarly the attenuation experiments with either serum are too few to form any valid conclusion.

Such, in bare outline, are the results of the serum prophylaxis of measles in the last London epidemic; in some respects they contradict the findings in previous epidemics and, as a whole, are to be viewed with some measure of disappointment.

It may well be that we cannot expect results much better than those described here until a satisfactory method of assaying serum potency is discovered. Nor can the scope of the prophylaxis be greatly widened until (*a*) immune serum is readily available at all times whenever required, and (*b*) deliberate exposure to infection is practised as circumstances permit, in order to secure for non-immunes the benefits of attenuation whenever circumstances permit. This procedure can only be justified if the efficacy of the serum has been proved beforehand. Written consent by parents or guardians should be regarded as imperative. Whether similar consent to the application of prophylactic measures is necessary when faced with a ward outbreak depends on the particular circumstances. While formal consent is always desirable the requirement may be dispensed with if it should entail delay which might prejudice the chances of success and hence the welfare of the patient. It appears reasonable to assume that when patients are admitted to hospital for treatment one is entitled to apply all recognized measures in the endeavour to avert or minimize the risks attendant on hospitalization. Omission to apply it might be held to constitute negligence. On the other hand, it is always essential to obtain consent previously if it is sought to confer immunity in the absence of known exposure. Probably this is the chief reason why active immunization experiments are so rarely attempted nowadays. It is possible that we may yet return to the pioneer methods of Home who, as long ago as 1759, claimed to have successfully vaccinated non-immunes with infective blood from measles patients, or to the bolder technique of Herrman who, in 1915, sought to maintain or enhance the inborn immunity of infants by daily instillation into the nares of fresh nasopharyngeal material from recent cases of measles. Three years later Nicolle and Conseil followed injection of convalescent serum by 1 c.mm. of blood freshly withdrawn from patients in the early stages of attack, while in the following year Richardson and Connor modified Herrman's method by supplementing the instillations by administration of convalescent serum. None of these procedures met with sufficient success to encourage their general application in measles prophylaxis but possibly they have not yet received adequate trial. The

limitations of immune serum by itself in the control of measles clearly invite investigation into the possibilities of active immunization methods.

In conclusion, I desire to thank Dr. J. A. H. Brincker, principal Medical Officer of the Public Health Department, London County Council, for placing most of the data in the paper at my disposal, and Mr. W. T. Russell of the Department of Epidemiology and Vital Statistics, London School of Hygiene and Tropical Medicine, for his advice and for his assistance with the statistical material.

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Section of Therapeutics and Pharmacology

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The Significance of the Excretion of Sex Hormones in the Urine

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ABSTRACT.—Recent work on the extraction and assay of urinary sex hormones is reviewed. The "sex hormones" known to be excreted in the urine are not identical with the hormones which have been actually isolated from the organs of secretion. Experimentally it is found that when active substances are administered only a very small proportion is excreted in recognizable form, and the excreted form may even be inactive. This general statement applies to œstrogens, androgens, progestin, and gonadotropic hormone. Hormone activity in the urine is, therefore, an uncertain index of hormonal activities in the body. However, with increasing knowledge of the chemistry and metabolism of hormones, methods of urine assay have been devised which give results capable of correlation with known or assumed physiological processes, notably in pregnancy and the normal menstrual cycle, and obvious effects are produced by certain types of tumour.

In the case of male hormone activity the lack of relation between urinary androgens and sexual condition has led to the assumption that the androgens in urine are largely derived from sources other than the gonads, probably from the adrenal glands. Work on this question is described in detail.

RÉSUMÉ.—Revue des travaux récents sur l'extraction et l'estimation des hormones sexuelles de l'urine. Les "hormones sexuelles" qu'on sait être excrétées dans l'urine ne sont pas identiques à celles extraites des organes sécrétoires mêmes. On trouve expérimentalement qu'après l'injection de substances actives qu'une très petite proportion seulement en est excrétée dans l'urine en forme reconnaissable, et que la partie excrétée peut même être inactive. Cette remarque générale s'applique aux oestrogènes, androgènes, à la progestine et à l'hormone gonadotrope. L'activité hormonale de l'urine est donc un index incertain de l'activité hormonale de l'organisme.

Quoique nous puissons nous attendre à une amélioration de cette situation avec l'augmentation de nos connaissances sur la chimie et le métabolisme des hormones et le développement de méthodes d'estimation dans l'urine, la valeur diagnostique des analyses hormonales est en général limitée aux états où l'organisme est inondé par un excès d'hormones, telles que la gestation et certaines tumeurs.

Description détaillée de travaux sur l'excrétion d'hormone masculine, et spécialement d'études par l'estimation biologique et chimique colorimétrique de l'excrétion de substances androgènes par des sujets normaux, des castrés des deux sexes, des eunuchoïdes, des cas de maladie d'Addison et des cas certains ou soupçonnés d'hyperplasie surrénale. L'absence d'interrelation entre les androgènes urinaires et l'état sexuel a mené à la théorie que les androgènes urinaires sont dérivées en grande partie de sources autres que les gonades, et probablement des surrénales. Dans deux cas de tumeur surrénale de grandes quantités d'androgène furent excrétées, et de la dehydroandrosterone fut extraite de l'urine.

ZUSAMMENFASSUNG.—Neuere Arbeiten über Extraktion und quantitative Bestimmung der Geschlechtshormone im Harn werden besprochen. Die "Geschlechtshormone", deren Ausscheidung im Harn bekannt ist, sind mit den aus den sezernierenden Organen isolierten Hormonen nicht identisch. Experimentell wurde festgestellt, dass nach Einverleibung aktiver Stoffe nur ein sehr kleiner Teil in identifizierbarer Form im Harn ausgeschieden wird und dass die Ausscheidung sogar in Form inaktiver Verbindungen stattfinden kann. Diese allgemeine Angabe gilt für Oestrogene, Androgene, Progestin und das gonadotrope Hormon. Die hormonale Wirksamkeit des Harnes ist somit kein zuverlässiger Massstab für Beurteilung der hormonalen Aktivität des Organismus.

Während mit weiterer Zunahme unsere Kenntnisse der Chemie und des Stoffwechsels der Hormone sowie durch Verbesserung der Harnanalysenmethoden eine Besserung dieser Sachlage zu erwarten steht, ist der diagnostische Wert der Hormonanalyse auf Zustände beschränkt, die mit einer Ueberschwemmung des Körpers mit Hormonen einhergeht, z.B. Schwangerschaft und gewisse Geschwulstarten.

Untersuchungen über die Ausscheidung männlicher Hormone im Harn werden ausführlich beschrieben u.zw. mit besonderer Berücksichtigung von biologischen sowie chemischen und colorimetrischen Untersuchungen über Ausscheidung von androgenen Stoffen bei Normalen, bei Kastraten beider Geschlechter, Eunuchoiden, Fällen von Addisonscher Krankheit und einwandfreien oder fraglichen Fällen von Nebennierenhyperplasie. Die Tatsache, dass keine Beziehung zwischen dem Androgengehalt des Harns und dem sexuellen Zustand besteht, hat zur Annahme geführt, dass die Androgene im Harn nicht aus den Geschlechtsdrüsen stammen, sondern aus anderen Organen, vermutlich den Nebennieren. In zwei Fällen von Nebennierengeschwulst wurden sehr grosse Mengen Androgen ausgeschieden und Dehydroandrosteron wurde aus dem Harn isoliert.

Introduction.—The problem of the significance of the excretion of sex hormones in the urine is far from being settled, and is, moreover, too wide and too complex to be covered in a short review. It is proposed, in the following paper, to examine critically certain general aspects of the subject as they appear to the chemical laboratory worker, and to illustrate these by an account of some of the work which has been carried out on one branch of the subject, urinary androgens, at the National Institute for Medical Research, in co-operation with my colleagues, Mrs. N. H. Callow, Mr. C. W. Emmens, Dr. A. S. Parkes, and a number of clinical collaborators. During the past year this work has formed part of a scheme undertaken by arrangement with the Hormones Committee of the Medical Research Council.

The nature of the sex hormones in urine.—In reviewing the history of work on the gonadal hormones, the impression is often given, generally unintentionally, that the discovery of physiological activity in the urine has been the first step in the direct path to the isolation of the hormone itself. As examples there may be cited the discovery by Aschheim and Zondek (1927) of œstrogenic activity in urine of pregnancy, which led to the extraction and isolation of œstrone and œstriol, or the discovery by Loewe and Voss (1929) of androgenic activity in male urine, leading to the isolation of androsterone. In fact, there is no evidence of the secretion of these particular compounds by the endocrine glands. Pedantically one might say that they were, therefore, not hormones, but compounds with hormone-like activity. It might be said that androsterone and dehydroandrosterone, isolated by Butenandt and his co-workers (Butenandt, 1931 ; Butenandt and Dannenbaum, 1934), so far from being sex hormones, were excretory transformation products which happened to have hormonal activity, and even, in the case of dehydroandrosterone, probably a product derived not from the male gonads but from the adrenal glands.

Reference to the formulæ in fig. 1 will illustrate the meaning of this distinction between primary hormones and excreted products. Of the natural œstrogenic compounds, α-œstradiol (Formula i), isolated by MacCorquodale, Thayer, and Doisy (1936) from sows' ovaries, and œstriol (Formula ii), isolated by Browne (1933) from Collip's placental extract " Emmenin ", are the hormones definitely known to occur in the body. Although Westerfield and Doisy (1937) have detected ketonic œstrogens in ovarian tissue, œstrone (Formula iii) has been isolated only from urine. Œstriol also occurs in urine, and was actually first isolated from that source. Œstradiols are found in the urine of the pregnant mare (Wintersteiner and Hirschmann, 1937), but the occurrence of œstradiol as an excreted product from the human body is only a supposition made on the grounds that a substance more active than œstrone or œstriol appears to be present. From these three compounds it would seem that the primary hormone, œstradiol, is converted by the body into the other two by oxidation, possibly in the course of acting. The next stage before excretion is that of conversion into water-soluble products by coupling with sulphuric acid or glycuronic

acid, a process which is the normal mechanism of the body for ridding itself of unwanted hydroxy-compounds.

The progestational hormone of the corpus luteum is progesterone (Formula iv), which has been isolated from sows' corpora lutea. The progestational activity of urine, blood, or placenta, is so small that no attempt has been made to isolate active compounds from these sources. Thus Loewe and Voss (1934) extracted only 1 rabbit unit of progestin activity from 20 litres of urine in the last quarter of the menstrual period or in the second month of pregnancy, and Bloch (1936) could not detect progestin in 500 c.c. of blood of pregnant women. Venning and Browne (1936, 1937), have shown that the excreted form of progesterone is the biologically inactive compound pregnanediol (Formula v). Progesterone therefore undergoes complete reduction and complete inactivation before excretion, in contrast to œstradiol. Other pregnane derivatives have been isolated from urine; thus Hartmann and Locher (1934-1935) found that the isomeric *allo*-pregnanediol accompanied pregnanediol, and Marker and his co-workers (1937 *a*, *b*, 1938) have isolated *epi-allo*preg-

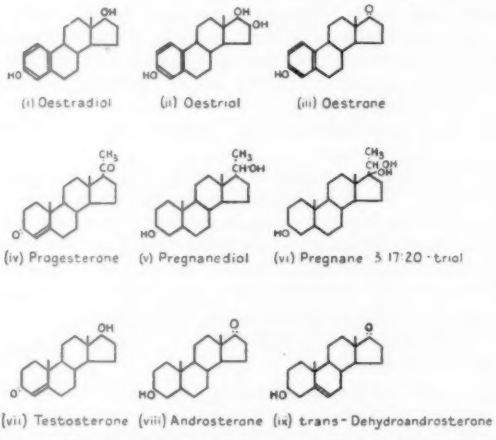

FIG. 1.—Formulæ of hormones and certain excreted products.

nanolone and two partly investigated pregnanetriols from pregnancy urine, whilst Butler and Marrian (1937) isolated pregnane-3 : 17 : 20-triol (Formula vi) from the urine of cases of adrenal hyperplasia. In the last case at least the urinary compound is more probably derived from the adrenal than from the corpus luteum.

Of the many androgenic compounds known, testosterone (Formula vii), isolated by David (1935; cf. David *et al.*, 1935) from bulls' testes, is the only one whose occurrence in the testis is established, though Ogata and Hirano (1934) have reported the isolation of another active, crystalline product from boars' testes. Androsterone (Formula viii) and *trans*-dehydroandrosterone (Formula ix), isolated by Butenandt from male urine, are commonly regarded as the excreted forms of male hormone. They are both active, but less so than testosterone. If we accept the assumption of derivation from testosterone, then the transformation in the body has been a combination of reduction at one position in the molecule with oxidation at another position. On the other hand, Butenandt and his co-workers have also (1937) isolated *epi*-ætiocholanediol, a completely reduced product, from male urine. The author also has isolated *trans*-dehydroandrosterone in very small amount from normal

female urine. The fact that *trans*-dehydroandrosterone is excreted in cases of adrenal tumour suggests the alternative that it is derived from the adrenal glands rather than from the gonads. This is not the occasion to enter into the chemistry of the adrenal glands, but a survey of the compounds isolated from ox adrenals by Reichstein and his school, by Kendall *et al.*, and by Wintersteiner and Pfiffner gives an idea at once of the complexity of the field and of the close relation of the adrenal family of compounds to the sex hormones. There are compounds with the side-chain in position 17 which have the same carbon skeleton as progesterone, and also compounds with the simple androstane skeleton. One of these latter compounds is itself androgenic, and a degradation product also has activity. We have here in these four groups a large family of chemically allied compounds produced in the ovary, the placenta, the testis, and the adrenal gland. Androstane derivatives are known to have multiple hormone activities (cf. Deanesly and Parkes, 1937), and if one further considers the possibilities of side-reactions by which related compounds may be produced as by-products, it will not appear surprising that œstrogenic and progestin activity is found in the testis, androgenic activity in the ovary, and œstrogenic, androgenic, and progestin activity in the adrenal (Zondek, 1934 *a*; Courrier, 1934; Dorfman, Gallagher, and Koch, 1935; Callow and Parkes, 1936; Parkes, 1937 *a*; Lipschütz, 1937; Seeman, 1937). If you consider how the estimate of the importance of a compound is conditioned by the ease with which it can be isolated, and the possible occurrence of unsuspected slightly active or inactive by-products, you will appreciate some of the difficulties and uncertainties of constructing a complete scheme of sex hormone metabolism and attaching precise significance to urinary sex hormones.

Hormone metabolism.—The number of independent variables which must be considered is very large. The processes which may go on in the body include absorption from the alimentary tract or from depots of oil solution injected intramuscularly; formation (whether by synthesis from simpler compounds or by degradation from sterols); more or less complete degradation of the formed hormone by reduction and oxidation, to some extent in the course of utilization; and esterification. The organs which may be concerned include not only the gonads and the accessory organs, but the adrenals, the liver, and the kidneys. Well may Siebke (1937), one of the veteran workers in this field, say:

> "We are absolutely convinced that the hormone assays carried out by us on excreta cannot give an exact idea of the general hormonal economy of the body. Too many unknown factors are acting: we do not know how much hormone is provided to the body by the food, how much is formed in the body itself, how much there is in circulation, and in what chemical form the hormone produces an effect on the appropriate organs; we do not know how much is stored, used up, and inactivated in one way or another; we fix on one figure alone, the fraction which is rejected. Even this figure we do not get by methods which are beyond criticism or absolutely exact; for, as far as concerns our own results, they deal only with determination of hormone which can be obtained by benzene extraction, but we do not know how many forms of hormone—perhaps soluble only in water—have escaped us in this process of preparation."

Survival of administered hormones.—One obvious test of the significance of the observed urinary excretion can be made, namely, the recovery from the urine of administered hormone. Luchsinger and Voss (1929) and Zondek (1934 *b* and *c*) made experiments of this kind. More detailed work was done by Robson, MacGregor, Illingworth and Steere (1934), and also by Kemp and Pedersen-Bjergaard (1933). The last workers investigated both fæces and urine in normal subjects, before and after oral administration of œstrin, and found that about 6% of the activity could be recovered from the urine. In a later study (1937), the administration of œstrin to men or castrate women was found to lead to the excretion of from 3–12% of it in the urine within the next two days, the proportion excreted being somewhat

greater after oral than after parenteral administration. Their method of extraction was, however, open to criticism, since they employed a mild hydrolysis which has not, in our experience, the effect of releasing all œstrin from its water-soluble combined form. Mazer and Israel (1936) also investigated the excretion of œstrin after administration, with the object of finding the "substitution dose of œstrogen, gauged by the minimal quantity necessary to maintain a premenstrual level of the principle in the blood and urine of castrated women" in order to judge amounts necessary for therapy. They may have been successful in this, but unfortunately for the question under discussion, they give figures only for the "active" œstrogen, i.e. the free œstrin extractable without hydrolysis. So far the result of work on human subjects has been not so much to provide evidence as to how hormones behave on passing through the body as to condemn methods of extraction. Only 3–12% of the administered hormone is extracted from the urine, but the percentage of the administered hormone which might be extracted is still unknown. Westerfield and Doisy (1937) have carried out experiments on the destruction and transformation of œstrogens in the monkey. They used a hydrolysis method (which is not described in detail) before extraction and found that only 1·5–5·3% of injected œstrogen could be recovered, even from an ovariectomized-hysterectomized monkey. The special interest of their work is the demonstration that œstrone and the non-ketonic œstrins are interconvertible in the body. Pincus and Zahl (1937) have investigated œstrin metabolism in the rabbit by more efficient methods which, they claim, lead to the recovery of up to 98% of the hormone under certain conditions. It is to be hoped that these methods can and will be applied to human urines. Until recently, the whole question of œstrin excretion seems to have been dominated by the unfortunate terms "active" and "inactive" forms of the hormone, with the implied assumption that the ratio of these is determined by the reproductive organs and not by some other organ such as the liver, one of whose supposed functions it is to esterify any excess of phenolic compound in the circulation, and thereby "inactivate" it solely in virtue of an acquired solubility in water and consequent rapid excretion.

Turning now to progestin, the state of affairs appears somewhat more satisfactory. It has already been mentioned that progestin activity is found in only minute amount in urine. There is, however, an inactive but chemically tangible transformation product, pregnanediol. Pregnanediol was first isolated from human pregnancy urine by Marrian (1929) (cf. Dingemanse *et al.*, 1930, and Butenandt, 1930). Later Odell and Marrian (1936) and Venning and Browne (1936) isolated pregnanediol glycuronide, and worked out analytical methods by which it could be recovered from urine (Venning, 1937; cf. Beall, 1937). Venning and Browne (1937) then demonstrated that it occurred in normal urine in the second half of the menstrual cycle, coincidently with the presence of the corpus luteum, and further, that injection of progesterone into human patients was followed by excretion of pregnanediol glycuronide, which could be recovered in an amount equivalent to from 12–46% of the progesterone injected. Here, therefore, we have a method of hormone assay which seems likely to be on a sounder basis than the œstrin assays.

No data have been published hitherto on the recovery of male hormone after administration to human subjects. We have ourselves obtained some results bearing on this subject in the course of investigations designed for another purpose. Under the auspices of the Therapeutic Trials Committee of the Medical Research Council a series of tests was carried out by several clinicians on the effect of androgens on prostatic hypertrophy. In an attempt to obtain as much information as possible, urine from the patients was assayed for androgen content before, during, and after treatment, extracts being assayed on capons by Dr. A. W. Greenwood at the Institute of Animal Genetics, Edinburgh. In the first stage of the trials, the material given was testosterone, in doses of 5 mgm. injected two or three times a week.

In this series (Table I) the differences in urinary androgen were small, and the figures must not be given too much importance, but it was certainly surprising to find that in some of the cases administration of testosterone appeared to produce an actual decrease in androgen excretion, apparently followed by a recovery after treatment

TABLE I.—ANDROGEN EXCRETION BY PATIENTS RECEIVING TESTOSTERONE

Patient*	Androgen content of urine (International units per day ; 7-day sample)		
	Before	During	After
Ca. C	17	11	14
Da. A	17	16·5	—
Far. C	10	9	—
Faw. B	17	22	—
Ja. B	—	16	24
Pa. C	10	12	—
Pr. A	13	? 9	9
Wi. A	10	10	23

* A, patients of Dr. J. Carver ; B, patients of Mr. V. W. Dix ; C, patients of Dr. Raymond Greene.

had ceased. Tentatively, one explanation which suggested itself was that a dep essant effect on androgen excretion was produced by way of the pituitary. Later cases were given larger doses of testosterone propionate instead of the free hormone. Table II gives data on cases treated by Dr. Raymond Greene. Here again the

TABLE II.—ANDROGEN EXCRETION BY PATIENTS RECEIVING TESTOSTERONE PROPIONATE

Patient	Androgen content of urine (International units per day ; 7-day sample)			Dosage of testosterone propionate when sample was taken
	Before	During	After	
Wee. ...	13 ...	? 9 ...	— ...	10 mgm./wk.
R. ...	11 ...	14 ...	— ...	20 mgm./wk.
T. ...	20 ...	21 ...	30 ...	20 mgm./wk.
Ca. ...	14 ...	15 ...	— ...	40 mgm./wk.
Wes. ...	? 9 ...	11 ...	? 8 ...	40 mgm./wk.
Be. ...	? 11 ...	13 ...	? 7 ...	50 mgm./wk.
Co. ...	17 ...	46 ...	— ...	50 mgm./wk.
Bo. ...	15 ...	54 ...	— ...	100 mgm./wk.

differences are small. With doses of 20 or 40 mgm. per week there are small increases, and only when 50 or 100 mgm. per week were given was there an unambiguous increase in the amount of androgen extractable from the urine, amounting to about 6% of the injected dose as a maximum in one case. Table III shows two results obtained recently with eunuchs, one treated by Dr. G. L. Foss, and the other under treatment

TABLE III.—ANDROGEN EXCRETION BY EUNUCHS RECEIVING TESTOSTERONE PROPIONATE

Patient	Date	Note of treatment		Androgen excretion: Capon assay i.u./day	Androgen excretion: Colorimetric assay mgm. "sterone"/day
S.	31.10.37 to 2.11.37	20 mgm. and 50 mgm. on 29 and 30.10.37	Free :	<4 ...	2·1
			Combined :	160 ...	30·7
,,	31.12.37 to 2. 1.38	After 5 weeks' rest from treatment	Total :	34 ...	8·4
C.	1.12.37 to 6.12.37	No treatment	Total :	9 ..	3·1
,,	29.12.37 to 2. 1.38	50 mgm./day	Total :	81 ...	11·6

by Dr. Levy Simpson. The first case, details of which have been published by Dr. Foss (1937), had a long history of intensive treatment with testosterone propionate over a hundred days ; calculated on the basis of the amount given just before the collection of urine, in the next two days some 16% of the administered activity was recovered by extraction from the urine. Seven weeks later, and five weeks after cessation of treatment, the urinary androgen extracted had fallen to 34 international units per day. It is not certain whether this was his basal level, since the prolonged effect obtained by injection of testosterone propionate in oil is most

pronounced. The second case, though receiving a higher dose, shows a still lower percentage recovery. The conclusion from these results is that, in general, the destruction and inactivation of male hormone in the body after absorption is so intense, and the yield of administered hormone recovered in the urine is so small, that the present method of urinary androgen assay is unlikely to give results which have any great significance in respect to the career of male hormone in the body.

Finally, before leaving the subject of hormone metabolism, reference must be made to the gonadotropic hormone. Zondek (1935) briefly reported that in human subjects injected with prolan, about 10% of the amount administered was excreted in the urine. Friedman and Weinstein (1937) have recently investigated the recovery of gonadotropic hormone from the urine of normal males receiving extract of pregnancy urine. Small doses produced no detectable increase in the gonadotropic activity of the urine, and only repeated injection produced an increase which was estimated at not more than 20% of the injected activity.

On the whole, therefore, the amount of the four types of sex hormonal activity which can be recovered in recognizable form in the urine after administration is so small, that it seems permissible to argue, on this evidence alone, that we cannot obtain in this way an accurate picture of sex hormone activity in the body in normal subjects, or in those suffering from minor hormonal disturbances.

The possibility of applying assays of sex hormones to the diagnosis of the commoner menstrual disorders and of pathological conditions in non-pregnant women is of considerable interest. For this purpose it is obviously necessary to know the state during the normal menstrual cycle, and a review of our knowledge of normal conditions throws a critical light on the dependability of hormone assay methods and on ability to detect abnormalities by excretion beyond the limits of normal variability. Space does not allow of a detailed review here, but reference to papers published during the last eleven years on œstrin excretion alone demonstrates the slowness with which agreement is being reached merely on the type of normal variation in relative amounts in the course of the menstrual cycle, whilst estimates of the absolute levels of normal excretion are widely different, although they show some signs, in recent investigations, of tending to a maximum.

Lack of sexual differentiation in hormone excretion.—Yet another angle from which hormone assays may be regarded critically is provided by the facts of excretion by one sex of hormones named after the other sex. In the earlier period of sex hormone research the simple theory was held by many that substances with male and female sex hormone activity were entirely characteristic of male and female organisms respectively, and there was a tendency to assume that these substances, apparently responsible, not only for obvious tasks in the reproductive system and for the production and maintenance of secondary sexual characteristics, but even for psychological phenomena, were segregated in the two sexes. The existence of hormones properly belonging to one sex in the organs or excreta of the other sex was announced with surprise and even resisted. For instance, Frank and Goldberger (1928) accepted with some reluctance the fact that œstrin occurred in male blood, and later (Frank, Goldberger, and McGee, 1928) speculated hopefully that the occurrence of œstrin in male blood "might offer a physical basis for homosexuality". Again, Laqueur *et al.* (1927), in reporting that they found œstrin in normal male urine, considered it necessary to say explicitly that they found it in urine from individuals "of whose 'manliness' there can be no doubt". The excretion of œstrone by the stallion (Zondek, 1934 *a*; Deulofeu and Ferrari, 1934 *a* and *b*; Häussler, 1934) is now so well known that it has become a "classical example". Without going further into the question, it may be mentioned that the administration of testosterone has been shown to increase œstrin excretion in men (Steinach and Kun, 1937 *a* and *b*). This observation, which seems to be confirmed by some figures of our own on eunuchs, suggests interesting possibilities in hormone metabolism.

Excretion of androgens.—The most obvious example of this lack of differentiation of the excretions of the two sexes is provided by the excretion of androgens. This has been the subject of investigation at the National Institute for Medical Research, and it is proposed to take this opportunity to report briefly on some of our results. Two other groups of workers, in Amsterdam (Dingemanse, Borchardt and Laqueur, 1937 *a* and *b*), and in Chicago (Gallagher, Peterson, Dorfman, Kenyon, and Koch, 1937), have been busy on the same subject, and our results are to some extent complementary and confirmatory.

Androgenic material in urine occurs in a so-called "inactive" form which is soluble in water and not extractable by benzene or other fat-solvents (cf. Adler, 1934). Sufficiently vigorous hydrolysis by acid liberates the steroid hormones from the water-soluble compounds, and one of the first steps has been to discover conditions under which the optimum yield is obtained. Both Dingemanse *et al.* and Gallagher *et al.* (loc. cit.) have investigated this point more or less systematically, and our own work has dealt with it in considerable detail. Once it had been established that the first factor necessary was a sufficient amount of mineral acid, series of experiments on samples from pooled urine have been carried out in which the time of hydrolysis at the boiling point was varied. Without hydrolysis at the boiling point the yield of androgen is negligible. Within the first half-hour the yield obtainable rises to a maximum, and then it falls, evidently owing to destruction. Peterson, Gallagher, and Koch (1937) (cf. Gallagher, Koch, and Dorfman, 1935) chose fifteen minutes, while we have adopted from half an hour to one hour as the optimum period. In other respects the method described elsewhere (Callow, 1936 *a*) is followed. However, judged by results, the Chicago method, the rather different Amsterdam technique, and our own method, give figures for normal urine which are of the same order of magnitude—a singular triumph in hormone assay. We have given attention to one matter which has not been considered by other workers, namely the effect of conditions of storage. After allowing male urine to stand at room temperature (10–15° C.) without preservative for a week, the loss of androgenic activity in one experiment amounted to 36%, and other more striking examples of loss of activity have been obtained. This is an important point in the collection of urines to be assayed for diagnostic purposes.

The assay of the neutral fraction of urine extracts for androgenic activity, referred to here, was carried out by Mr. C. W. Emmens using the method of injecting capons and measuring the comb growth produced, according to the technique described by him in detail elsewhere (Emmens, 1938). Comparison with androsterone, the international standard of male hormone activity, is made by means of a dose-response curve constructed from the stock of capons receiving standard doses of androsterone; at least one control group of five capons being injected with androsterone over the period during which assays of urine extracts are being made.

Recently (Callow, Callow, and Emmens, 1937) we have investigated the colour reaction with *m*-dinitrobenzene, first proposed by Zimmermann (1935) for male hormones and later applied to the estimation of hormones in urine extracts by Zimmermann (1936), by Wu and Chou (1937), and by Oesting (1937). We have considerably increased the sensitivity of this reaction by modifying it, and an amount of extract equivalent to 10 ml. of a normal urine is sufficient to give an easily measurable colour; we have been able, by analysis of the colour, to increase the specificity of the test, and by correlation with capon assay we have been able to raise it to the status of a good index of androgenic activity.

Examination of the approximate absorption spectra of the colour reactions given by the steroid sex hormones and related compounds demonstrates that, in interaction with *m*-dinitrobenzene and potassium hydroxide, compounds of one particular class give a strong absorption band in the green, namely the 17-keto-compounds, among which are androsterone and dehydroandrosterone, the known androgenic constituents

of urine. Androstadien-17-one and androstan-17-one, for specimens of which we are indebted to Dr. R. L. Warren of the Royal Cancer Hospital, give similar curves. As a convenience, results are expressed in terms of milligrammes of " sterone " per litre of urine or per day's output of urine, the name " sterone " being a non-committal term for a 17-keto-compound like androsterone or dehydroandrosterone without specifying exactly what it is. In fig. 2 the values of this colorimetric assay are plotted against values from capon assay for a very varied collection of urines. Normal male or female urines are shown by the solid or half-moon points respectively. The line has been fitted by my colleague, Mr. Emmens, and has the equation $y = 6{\cdot}4x - 16{\cdot}7$, where y = content of international units by capon assay, and x = " sterone "

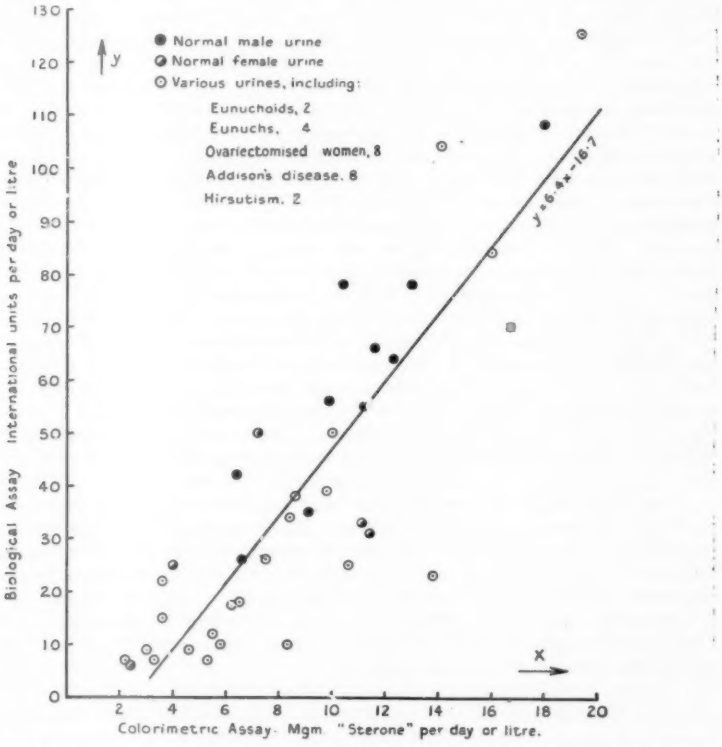

FIG. 2.—Relation between capon assay and colorimetric assay for urine extracts from various sources.

content measured colorimetrically. Were the only androgenic and chromogenic constituent of the urine extract pure androsterone, the equation would be $y = 10x$, and were it pure dehydroandrosterone it would be $y = 3x$. The position of the experimental line suggests that there is a biologically inactive, but chromogenic, impurity in the extracts, and that, apart from this, the androgenic material is a mixture of substances chemically and biologically resembling androsterone and dehydroandrosterone. Neither the biological nor the chemical tests are sufficiently specific for a more definite statement to be made ; obviously the occurrence of related

androgenic and chromogenic compounds cannot be excluded. It seems probable, from some recent preliminary tests, that chromogenic but biologically inactive substances may be removed by extraction with benzene before hydrolysis, and that the extract then obtained after hydrolysis may give a yet closer relation between colorimetric and capon assay. A detailed account of this investigation will be published with Mrs N. H. Callow and Mr. C. W. Emmens.

The feature of practical interest which appears in this diagram is that, in spite of its being made up from several classes of urines, the sources of which are sharply differentiated physiologically, it is impossible to distinguish segregation of any particular class into a group. One reason for this may be the multiplicity of factors influencing the androgen excretion of individuals. Dingemanse *et al.* have shown that there is a variation of urinary androgen with age. Before puberty and in senility androgen is present, but in small amount; the largest amount is present in the sexually active adult. Chou and Wu (1937) report that the male hormone excretion of Chinese is higher in the summer than in the winter, but as their results are based on colorimetric assays unchecked by capon assay, they require confirmation. It may be that constituents derived from the food interfere with the estimation. Dingemanse *et al.* and Gallagher *et al.* found large differences between individuals, and, further, wide variations in the daily excretion by the same individual. Our own examinations of subjects believed to be free from sexual dysfunction entirely confirm the existence of a large variation in the excretion of individuals from time to time. Thus, seven consecutive collections, each over three days, of urine from a male, aged 36, diagnosis hæmatemesis, showed daily levels, in mgm. of "sterone" per day, of 6·2, 6·9, 10·0, 9·0, 9·1, 7·2, 10·6. A second male patient, aged 38, diagnosis melæna, in six consecutive collections, each over six days, gave the figures 3·5, 8·3, 10·8, 12·3, 9·8, 8·6. The collection of these urines was kindly arranged for us at the Middlesex Hospital, by Professor E. C. Dodds. Women show equally high variability. Although Dingemanse *et al.* found in a single case that the highest excretion occurred during the post-menstrual period, Gallagher *et al.* did not confirm the existence of cyclic variation. Our own results indicate a tendency in the direction of higher values at the beginning of the cycle, but we have not yet sufficient data to be able to say whether this behaviour is general.

Bearing in mind the uncertainties which are introduced by these wide limits of variability in the normal subject, we may consider again the possibility of distinguishing between subjects grouped according to certain obvious physiological abnormalities. Tables IV and V show the distributions with respect to androgen excretion, expressed either in international units (capon assay) or mgm. of "sterone" (colorimetric assay) of patients classified according to their physiological state. These are preliminary data obtained in investigations which, when completed, my colleagues hope to publish in detail.

TABLE IV.—DISTRIBUTION OF LEVELS OF ANDROGEN EXCRETION IN THE URINE OF VARIOUS TYPES. BIOLOGICAL ASSAY.

Androgen excretion (international units per day or per litre)	< 10	10—19	20—29	30—39	40—49	50—59	60—69	70—79	80—89	90—99	100—109	110—119	> 119
Normal females (5)	1	—	1	2	—	1	—	—	—	—	—	—	
Normal males (6)	—	—	1	—	1	—	1	2	—	—	1	—	
Eunuchoids (3)	—	—	—	1	—	—	—	—	1	—	1	—	
Eunuchs (5)	1	2	1	1	—	—	—	—	—	—	—	—	
Ovariectomized women (12)	4	5	1	—	1	—	—	—	—	—	—	1	
Addison's disease (6)	2 (♀)	1 (♂)	2 (♀) 1 (♂)	—	—	—	—	—	—	—	—	—	
Hirsute women (13) ? adrenal hyperplasia)	3	1	—	1	2	—	2	1	1	—	—	1 [+ 2 cases; adrenal tumour. 150-2,500 i.u./day and 220 i.u./day]	2

TABLE V.—DISTRIBUTION OF LEVELS OF ANDROGEN EXCRETION IN THE URINE OF VARIOUS TYPES. COLORIMETRIC ASSAY

"Sterone" excretion (mgm. per day or per litre)	< 2·2—3·9	4—5·9	6—7·9	8—9·9	10—11·9	12·—13·9	14—15·9	16—17·9	18·—19·9	
Normal females (7)	2	2	2	1	—	—	—	—	—	
Normal males (10)	—	—	3	3	1	2	—	1	—	
Eunuchoids (3)	—	1	—	—	—	1	—	1	—	
Eunuchs (4)	1	—	—	2	—	1	—	—	—	
Ovariectomized women (14)	1	4	5	1	2	—	—	—	1	
Addison's disease (6)	2 (♂) 1 (♀)	1 (♀)	2 (♀)	—	—	—	—	—	—	
Hirsute women (12) (? adrenal hyperplasia)	1	1	2	1	1	—	1	1	—	[+ 2 cases; 27 and 33; + 2 cases adrenal tumour, 150 and 175 mgm./day]

Normal women (in the top line) vary between limits of excretion of 5 and 60 international units of androgen per day. Normal men (in the section immediately below) vary between the limits of 20 and 110 international units of androgen per day. As a group, the women have a lower level of excretion than the men, but the limits overlap, and it is impossible to distinguish one sex from the other from examination of the urine by these methods. There is a school of thought which considers that such a difference between the sexes ought to exist; even if the quantity is the same, some qualitative difference should exist. At present, no characteristic difference can be discerned, although, admittedly, our methods of chemical examination are not highly selective. It is still possible, however, that with increasing specificity, analysis may show some differentiation. Referring to the other sections of the diagram, it can be seen to what a small extent androgen excretion is dependent on the sexual condition.

Eunuchoids [two of these are patients under the observation of Dr. Crooke, and particulars of one of them, S.A., have been published (Crooke, 1937)], in which testicular function appears to be completely suppressed, would appear to have an androgen excretion which is, if anything, above the average for normal men. Eunuchs, of which there are four examples, show a low level of androgen excretion, but not necessarily outside normal limits.

These cases remove the uncertainty as to whether the castrated male excreted significant amounts of male hormone. Chou and Wu (1937) reported definite androgenic activity in both capon assay and colorimetric assay in the urine of a eunuch aged 68, but McCullagh and Renshaw (1934) had previously failed to find androgen activity in the urine of eleven eunuchs; Koch (1936) reported low positive results, but later Kenyon *et al.* (1937), using an efficient method of extraction, found only traces in two cases, amounting to 1 i.u./litre in one case and 3·5 i.u. in another. It might be conjectured that possibly decomposition had occurred in the course of making the large collections to which they refer. After some unfortunate experiences, we consider it most important that urine should be extracted as fresh as possible, even if a preservative has been added. Two of our five cases, one under Dr. S. Levy Simpson and the other under Dr. P. M. F. Bishop, show values well within normal limits without having previously received any hormone therapy, although the colorimetric assay figure (13·8 mgm./day) in the latter case is anomalous. A third is, perhaps, suspect on account of his male hormone treatment. The medical history of the remaining two is less well established.

Ovariectomized women (mostly patients under the observation of Dr. Levy Simpson) form a group, with one exception, definitely below the average of normal women but still overlapping the normal limits. Consideration of these three groups seems definitely to exclude gonadal function as a major factor in determining androgen excretion. Turning, for reasons I have already mentioned briefly, to the adrenal as a possible site of origin of urinary androgens, we obtained, through the agency of

Dr. Crooke and Dr. Levy Simpson, urine from a number of cases of Addison's disease. On the whole, the low level of androgen in most of these cases gives support to the hypothesis suggested. Unfortunately, complete adrenalectomy is not a possible operation in the human, and the degree of adrenal cortical deficiency in these patients is difficult to assess.

When, however, we turn from deficiency to excess, and consider cases of suspected adrenal hyperplasia included in the remaining class of subject, cases of hirsutism, we come to a series of observations which lead on to the part of this investigation which seems most likely to bear fruit of more than academic interest. Simpson, de Fremery, and Macbeth (1936) examined a series of cases of adrenogenital syndrome and found in the urine of four out of seven cases a significant excess of androgen, though in only one case was this very large. Since then, Slot (1936) has recorded a case of virilism, due to adrenal tumour, with an excretion of 2,200 i.u. androgen per litre of urine. Kenyon *et al.* (1937) (cf. Cahill *et al.*, 1936) have recorded an excretion of 480 international units per day in a case of carcinoma of the adrenal cortex.

With the co-operation of several clinicians, we have investigated the androgen excretion in a series of cases which showed signs, in varying degrees, of virilism, hirsutism being the common symptom. It will be seen that the range over which the figures for androgen excretion spread is a wide one, stretching from 7 i.u. per day for an aged woman up to values which are outside the limits of the diagram. Considering the moderate figures, our results are entirely in accord with those of Kenyon *et al.*: that as a rule normal amounts of androgenic material are excreted, but that a moderate excess of androgens is occasionally found. One of these cases, with normal excretion, has been operated on recently, and an apparently normal adrenal was found and removed. In another case with moderately high androgen (about twice normal) an enlarged adrenal has been diagnosed by X-ray examination. Dr. Crooke considers that in his series of patients there is some correlation between high androgen excretion and degree of menstrual disturbance. On the whole, however, it is difficult to find any line of demarcation or to suppose that hirsutism is due only to a hypersecretion of an androgen which can be recognized in the urine. The dividing line comes at a much higher level, and in an entirely separate category come two cases of adrenal tumour. In one case, from the London Hospital, the patient was a girl aged 7 years, with a large adrenal tumour which, removed at autopsy, weighed 5 kg. At one stage, the urine contained 3,500 i.u. of androgen per litre. A few weeks later a specimen had, by capon assay, 500 i.u. per litre and, by colorimetric assay, 170 mgm. of "sterone" per litre. 70% of the androgenic activity could be accounted for by dehydroandrosterone, which was isolated in pure crystalline form (Callow, 1936 *b*). Recently, the urine from a second case, a 19-year-old girl from whom an adrenal tumour was removed by operation, has been examined. This showed an androgen excretion of 320 i.u./litre by capon assay, and a colorimetric assay of 140 mgm. of "sterone" per litre. Dehydroandrosterone was again readily isolated from the urine in a yield of about 60 mgm. per litre. Adrenal tumour can, therefore, be readily and quickly diagnosed with the aid of androgen assay, either colorimetric or biological, of the urine.

A contrast to these cases was provided by a case of Cushing's syndrome in an adult woman, studied clinically by Dr. Crooke. This case showed hirsutism of male type, but we were unable to detect any hormonal abnormality in the urine, and the androgen excretion, in particular, was within normal limits and actually lower than the normal average. At autopsy the adrenals were of normal size.

The andrenogenital syndrome is comparatively rare in men. Burrows, Cook, Roe and Warren (1937) found in the urine of a man with an adrenal tumour a very high œstrogen content, with a moderately high androgen content. They isolated from the urine the compound androstadien-17-one, closely related to dehydroandrosterone.

The occurrence of high œstrin excretion in cases of adrenal tumour has been reported by Frank (1934, 1937), Graef *et al.* (1936), but the enormous amounts reported by these writers do not seem to be a constant occurrence (cf. Slot, 1936). Of our own cases, subject to the reservation that œstrin extractions have not always been efficient, it can be said that the child certainly excreted excessive œstrin for her age, but did not give an extraordinary value, and in Dr. Levy Simpson's case there is no indication of an obviously excessive amount.

The fact that only in cases of adrenal tumour is an enormous excess of androgen found, and that the principal active compound is dehydroandrosterone, leads to the assumption that the dehydroandrosterone found normally is an excretory product derived from the adrenals, and even suggests that urinary androgens are derived entirely from this source. I doubt whether this latter general conclusion is justified, for it seems possible that the adrenals and the gonads are, to some extent, complementary to each other in androgenic activity. The question of the source of androgenic substances in the urine has recently been reviewed by Parkes (1937 *b*). The complex question of the relation between the adrenals and the gonads is outside the scope of this paper.

There appears to be a definite relation between the pituitary and androgen excretion, whether derived from the adrenal or the gonads. Davidson (1937) found that some development of the atrophic prostate and seminal vesicles of castrated rats could be brought about by the administration of adrenotropic extracts of the pituitary. We have been able, by the courtesy of Dr. W. D. Henderson, of the National Hospital, Queen Square, to examine the urine from a case of infantilism due to pressure on the pituitary in a youth aged 22. Before operation the urine extract had a low colorimetric titre, and the capon assay showed the presence of a trace only of androgen. A month after operation these values had notably increased, and still later, at least as regards colorimetric assay, the androgen excretion appears to be normal, not only in amount, but also in its chemical character; the colour reaction had previously been rather anomalous.

In conclusion, the present state of the question of the significance of the excretion of sex hormones in the urine may fairly be summed up by saying that in cases where relatively tremendous amounts of hormone are produced and excreted, hormone assay is an extremely valuable aid to diagnosis. In quite another category, with our present methods, and even perhaps with improved methods, are the mildly abnormal cases. I think that the assumed significance of urinary sex hormone estimation in such cases must be justified empirically. If we know definitely that in a certain physiological state a given sex hormone is produced in large amount, and we find a corresponding product in the urine, then a connexion is established, and it will be possible to extend to other circumstances an argument based on analogy. Argument in the other direction, from observed excretion to a process in the body, is unsafe in the present state of our knowledge. Here, I think, it is appropriate to quote R. T. Frank and his colleagues (1934) who, summing up nine years' work on hormone assays, say that "such studies, though they serve as valuable aids, cannot replace clinical acumen and experience".

It is to be hoped that such improvements in methods of extraction and assay may result from the work of chemists and biochemists that some material advance may be made from the present position, and more certain aid be given to the clinician.

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Discussion.—Dr. LEVY SIMPSON said that the investigations of Dr. Callow and his colleagues were, he believed, of fundamental importance, and should ultimately throw a good deal of light on the biological mechanism in endocrinopathies. At the moment, the significance of the data was not always clear, but the apparent confusion in some directions should serve as a stimulus for further study.

In 1933 (*Proc. Roy. Soc. Med.*, 1934, **27**, 383), he began investigations, in collaboration with de Fremery and Macbeth, on the "male" comb-growth, seminal vesicle, and prostate-stimulating hormone, in the urine of virile women. The detailed results were subsequently published (*Endocrinology*, 1936, **20**, 363), and, in summary, showed that patients with the adrenogenital syndrome, or the Cushing's syndrome, might—but did not invariably—excrete an excess of "male" hormone. The lack of consistency was perhaps difficult to appreciate if excretion was a measure of secretion, but this latter was probably not the case. The innate responsiveness or refractoriness of the tissues was also a factor. Since the pituitary did not secrete comb-growth hormone, and since one of the worst cases of adrenal hirsutism had followed bilateral ovariectomy, it seemed probable that the adrenal gland was responsible for the secretion of the excess of comb-growth hormone. Subsequent experience with adrenal tumours, and the disappearance of pathological hormones after their removal, tended to confirm this view, as also did the work on castrated males and females recorded by Dr. Callow.

Clinically, the presence of a gross excess (e.g. more than 300 capon units per day) of comb-growth hormone in the urine of a virile woman was of diagnostic significance, and meant that every effort, including laparotomy, must be employed to track down an adrenal tumour. Unfortunately, adrenal hyperplasia was occasionally associated with values up to 300 units per diem, but more usually the excretion was no greater than 150 units. Gross enlargement of the clitoris favoured the diagnosis of an adrenal tumour, but this was not invariable; and such enlargement might be absent even when an adrenal tumour was present, together with an excess of comb-growth hormone in the urine.

In a male with an adrenal tumour and feminization, including enlargement of the breasts and atrophy of the penis, with impotence, a large amount of œstrogenic hormone was found; this disappeared after operation, but reappeared when metastases occurred. It was, in fact, the first evidence that secondary deposits were occurring. Why should an adrenal tumour in the male appear to give rise to an excess of œstrogenic hormone, and, in the female, to an excess of the comb-growth hormone? At his request, Miss Joan Ross had kindly compared two such tumours, and found that, although the histological appearances were similar, that of the female contained certain characteristically staining discrete granules, which were not present in that of the male. She also observed that similar granules appeared in the inner layers of the adrenal cortex in normal males after puberty, but did not appear in normal females until the age of 50. There might, therefore, be a histological basis for these biological differences.

In a series of ovariectomized women, investigated with Dr. Callow and colleagues, it had not yet been possible to correlate the clinical types with the biological findings. Apparently in the case both of ovariectomy, and of castration in the male, the changes that resulted were dependent upon the initial endocrine constitution of the individual, and considerable differences were met with. Some of the women excreted amounts of comb-growth hormone above normal, but it did not follow that these women showed virilism or hirsutism, to an appreciable degree. It would appear that here, too, the response of the tissues to circulating hormones was an important factor determining the clinical manifestations.

Dr. A. S. PARKES: The original work described by Dr. Callow has been carried out as part of a plan of investigation into the whole subject of the practical possibility and clinical value of what is usually called "hormone analysis". In the course of this work it has become evident that the technical difficulties of obtaining sound results are very great, and that the significance of the results is not yet obvious. However, as will have been gathered from Dr. Callow's admirable survey, considerable progress is being made, even though much of it

is negative in character, and it is to be hoped that conclusions of practical value will ultimately emerge.

Dr. Callow has emphasized that many of the substances commonly termed hormones are more likely to be of the nature of by-products in the metabolism of other substances. I think, however, that it is difficult to draw any sharp line of distinction between hormones and waste products. There is evidence that the substances we now know as hormones were originally waste products for which animals, in the course of evolution, have acquired a use. Some of the substances which function as hormones in mammals occur in lower vertebrates in conditions in which they can, presumably, be of no value. Thus, the lactogenic hormone, probably responsible in mammals for the secretion of milk, is to be found in the pituitary gland of birds, reptiles, amphibians, and fish. We have heard of the extraordinary mixture of œstrogenic and androgenic substances in both sexes of mammals, and notably in the urine of men and women. If evolution proceeds along the line which it appears to have taken so far, and mammals learn to use these anomalous substances, it may perhaps be prophesied that evolution will be in the direction of general intersexuality.

Section of Ophthalmology

President—W. H. McMullen, O.B.E., F.R.C.S.

[*January* 14, 1938]

DISCUSSION ON THE DETERMINATION OF DISABILITY RESULTING FROM INDUSTRIAL INJURIES AND DISEASES (EXCLUDING MINER'S NYSTAGMUS)

Mr. P. G. Doyne: I have held the post of medical referee for ophthalmic cases to a good many of the county courts of London for some years. The work of a medical referee consists in sitting with the judge as assessor in court, or in examining persons sent by the court for a report "as to their condition and fitness for employment, as to what kind of employment, as to whether, or as to what extent, the alleged incapacity is due to the accident"; also in approving, from the medical point of view, cases in which a settlement has been made. Sitting as assessor forms the major part of the work.

The Workmen's Compensation Act is solely concerned with the earning power of the workman. It takes no regard of the economic state of the labour market or of the physical condition of the workman produced by an accident, provided that this has not reduced his earning power. There is one exception, however—disfigurement is taken into consideration in making the award.

Now loss of an eye is one of the most frequent causes of dispute. Under the Act, the workman gets no compensation for the loss of the eye, *per se*, but only as it affects his working capacity and so his earning powers. With a well-fitting glass eye there may be no disfigurement. After time has been allowed for him to become adjusted to the one-eyed state—six months is usually considered adequate—he is adjudged fit for ordinary labouring work and payments are stopped. Many labourers, particularly those working in the London docks, are engaged by the week or by the day. It will be known locally that they have lost an eye and this may—at any rate in their opinion—militate against their being taken on, particularly if work is slack.

The law provides no loophole here and this accounts for much continued litigation and for such factors as persistently discharging sockets and various forms of anxiety states and so forth, which have an intentional, or psychological, basis. I have in mind the case of a youth who had had an eye excised after a penetrating injury. After six months the insurance company brought the matter to court for final settlement. The youth complained that he was not fit to go back to work. The socket was painful and discharging, he could not sleep, suffered from headaches, and so forth. His panel doctor, in answer to a question from the judge, admitted that in his opinion the best thing for the youth was to go back to work . . . "but", he added, "of course he can't go back in his present condition". Rather a contradiction in terms! I have seen marvellously speedy recoveries of irritable and discharging sockets and conjunctivæ once a lump-sum settlement has been arrived at, and I am not at all certain that in the majority of these cases the workmen were consciously malingering.

With regard to loss of an eye, I think that the disability, after time has been given for adjustment to the one-eyed state, is not at all great. Those who were at the Oxford Congress last year will remember the description by a one-eyed flying man of

his reactions when flying, landing, &c. There have been one-eyed ophthalmic surgeons, and surely steering a Graefe knife across the anterior chamber of the eye is a pretty severe test! Nelson found that the possession of a blind eye actually had its advantages. I think, myself, that probably in many respects one is better off with only one eye than with two eyes and bad muscle balance. It allows one to exploit an inferior mechanism for depth-perception to the full rather than a superior mechanism imperfectly. The great disadvantage of having only one eye is that one has "all one's eggs in one basket". Many county court judges always grant a declaration of liability in cases of loss of one eye. This, in effect, postpones a complete settlement indefinitely and allows the case to be reopened under the Act if trouble occurs in the remaining eye.

I will next refer to a type of case which I would group under the heading "Manifestation of the Refractive Error". Anyone who worked in the Ministry of Pensions immediately after the Great War would be familiar with these cases. How often one is faced with a record of "right and left $\frac{6}{6}$" on joining up, when in fact there are conditions present which, though easily comprehensible to the medical mind as accounting for defective vision in one or other eye, are difficult to substantiate in court. "A good man struggling in adversity" is the ophthalmic witness trying to uphold a diagnosis of amblyopia ex anopsia, before judge and opposing counsel.

However, with regard to "manifestation of the refractive error". I believe that the majority of the individuals are quite honest in their protestations. I have in mind the typical case of a coal-miner, aged 55, who had worked in the Kentish coalfield all his life. While he was working, a fragment of coal had got into his right eye producing a small superficial ulcer downwards and outwards from the centre of the cornea, not quite involving the pupillary zone. This rapidly healed, leaving a faint corneal nebula 2 mm. in diameter. The man complained that since the injury the vision of both eyes had become seriously affected. True enough, it was less than $\frac{6}{60}$ in each eye. Examination revealed no abnormality apart from the corneal nebula. There was, however, myopia (over 5 diopters) in each eye, and with appropriate glasses vision was brought up to $\frac{6}{12}$ right and $\frac{6}{6}$ left. The man had never worn glasses and had never felt the need for them. Counsel actually claimed for him as an alternative plea that the injury had made the refractive error manifest to him. An unanswerable plea it seems to me.

In conclusion: I have been impressed with the often devastating effect of a central corneal nebula upon epicritic vision, however faint the nebula may be (and this where no question of compensation is arising and therefore no ulterior motives can be present). The medico-legal consideration of these cases presents great difficulties. Protopathic vision is unaffected and the visual fields are full. One must, of course, base one's estimate of the resulting disability upon the nature of the man's work. But to decide how much vision, in terms of the test types, is necessary for, say, a coal-trimmer to do his work adequately, is not an easy matter.

Mr. John Foster: *Residual disability and suitable employment.*—The following rather disconnected observations are part of five years' notes, collected for addition to an existing work on the Ophthalmic Section of the Workmen's Compensation Act:—

While the limitations or depth-perception and field of vision of the one-eyed state are well recognized, the residual disability value to workmen of a lost eye varies in the North of England between fifty and one hundred and fifty pounds. The actual return to the old work, however, is often complicated by the danger to the remaining eye from flying fragments, and while admittedly many men are capable of the work, it is regarded as unsuitable, for this reason. Disputes on this point have often gone as far as the Court of Appeal, with varying results and with actual disagreement amongst learned judges on the same case.

TABLE I.

WORK HELD TO BE NOT SUITABLE.	WORK HELD TO BE SUITABLE.
Coal Face Eyre *v.* Houghton Main Colliery, 1910	*Blacksmithing* Moulton *v.* Salt Union Ltd., 1909
Stonebreaking Petrie v. Weir, 1900. 2 F. 1041. 1900	*Boilermaking* Morton and Co. *v.* J. W. Woodward, 1902
Collier Jackson *v.* Hunslet Engine Company. 1916. 2 K.B. 8; 9 B.W.C.C. 269	*Collier* (coal face) Cawdor and Garnant Collieries, Ltd. *v.* Jones

Some years ago I made an attempt, by having questions asked in Parliament, to find out how many men who had lost an eye actually returned to their old job, but the Board of Trade had no figures available.

The crux of the whole situation depends upon the wearing of goggles. I find that all trades are now accepting the fact that goggles can be worn at work—except at the coal face. In an attempt to deal with this situation, which turns every miner who has lost the sight of one eye into a labourer, an indemnity company in the North of England has several times presented the following statistical table in court (Table II.)

This table purports to show that the chances of losing a second eye by a flying fragment are one in four thousand, and that the chances of being killed are five times as great as those of losing a second eye.

TABLE II.—LOSS OF EYES IN COLLIERIES.

Statistics of the local Indemnity Company:—

Year	Miners in work	Eyes lost	Deaths
1929	93,000	37	101
1930	93,000	31	138
1931	89,000	29	132
1932	100,000	49	118

The loss of an eye means total loss, or reduction of vision below $\frac{6}{60}$.

Professor Mainland of Dalhousie University, to whom I submitted this table, made the following comments about its validity: (1) That in some of these cases both eyes may have been lost simultaneously. (2) That these figures represent not only miners below ground, but some of those who before and after accidents are working above. (3) That strictly speaking, one would actually have to follow the fortune of one-eyed men at work at the coal face, before one could pronounce definitely on the relative risk.

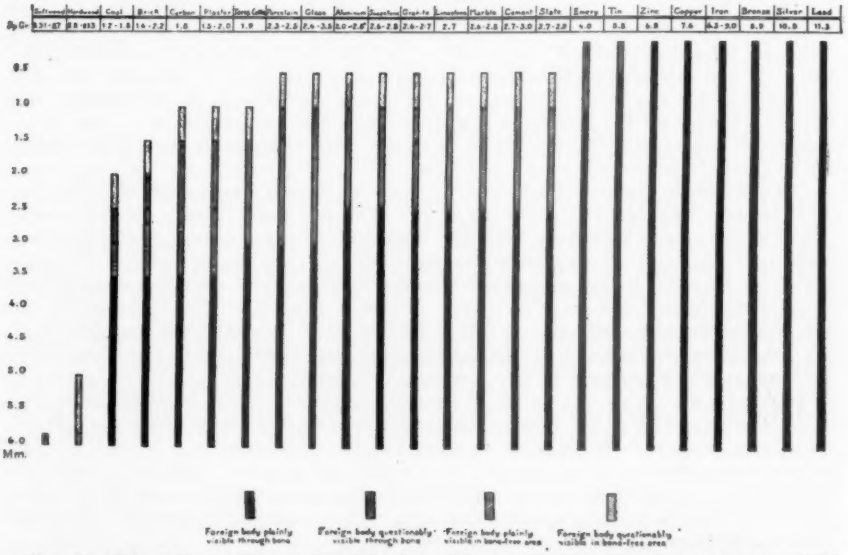
It would seem, however, that the table gives grounds for suggesting that the risk is, at any rate, not a great one. Even so, I do not think one should recommend the one-eyed man to face fragments of flying coal without some protection. If only miners would wear goggles at the coal face, the risk would at once be reduced to something very small indeed. If one suggests this, however, a series of objections are raised, some by the miners and some in court. Amongst them are: (1) That goggles at once become misty in the pit. (2) That they become covered with coal dust, and that a man cannot carry a handkerchief with him to be always cleaning them. (3) That there is a rule against men wearing goggles in the pit. (4) That if a man is a deputy he must necessarily be better than the men around him in all respects, and that the wearing of goggles would at once be a tacit admission that he was inferior to his subordinates. (5) That no form of goggles is an adequate protection, and there is no precedent. The curious thing is that boiler-makers in the lower chambers of a ship will definitely refuse to work without this protection in atmospheric conditions very similar. The suggestion that there is a rule against the wearing of goggles is, of course, fantastic.

The cleaning of goggles can be performed by a movement of the fingers and thumb alone, and steam does not cover them for more than half a minute of "walking

along the roads "; as soon as the temperature of the goggles, and that of the surrounding air become the same, condensation ceases. I have worked in goggles at the coal face for a couple of hours, and found them an adequate protection. They are, however, not a very effective protection against fragments, which can get round the edge when one is cutting away the roof of a seam (holing in). American miners seem to employ goggles extensively, and they certainly have been in use successfully at the Shaw Cross Pit, Dewsbury, where I attempted my investigation. I know of no other firm, however, which is employing them.

Irremovable intra-ocular foreign bodies.—During the last few years I have noticed increasing difficulty in removing intra-ocular metallic foreign bodies. This, I suspect, is due to the alteration in the magnetic quality of the type of steel being used. During the War it was found that fragments of grenade casings which contained manganese were only slightly responsive to magnetic attraction, and it was also made manifest that, while a large quantity of silica or aluminium mixed with steel reduces the magnetic quality of the metal, a small amount of either of these materials increases it. It is, I suspect, the increased use of manganese in tool steel which is responsible for our difficulty in this matter. With the increasing use of spectacles by skilled workmen, the radiologist's ability to detect fragments of glass in the interior of the eye becomes more important. Many radiologists still deny that ordinary (crown) glass, which contains lime and silica, and in certain cases barium, will show against bone on an X-ray plate. Lead glass which, of course, shows very readily, is only found in the "flint segments", and bi-focals of the "Kryptok" type, or, certain lenses for myopes, not much employed in this country. Nevertheless, I have been able to obtain a positive result occasionally, and the actual permeability of these glasses has been worked out under conditions resembling the anatomical, by Spackman. The graph (Table III) shows that the ability to detect the glass depends upon the combined factors of the size and composition of the material.

TABLE III.



Reproduced from the *Archives of Ophthalmology*, 1937, n.s. **18**, 231. "Localization of intra-orbital foreign bodies", by Edgar W. Spackman, M.D., D.Sc.(Med.) With acknowledgments to the American Medical Association.

The actual localization in the eye in difficult cases of a piece of steel will always be determined finally by the magnet, but when this has failed the X-ray localization is of great importance in deciding the prognosis. All methods based upon the standard eye (amongst them Sweet's) are open to a great fallacy, since even an emmetropic eye can vary one to three millimetres length from the standard (Wessely, personal communication). I have been employing the Wessely prosthesis for localization for

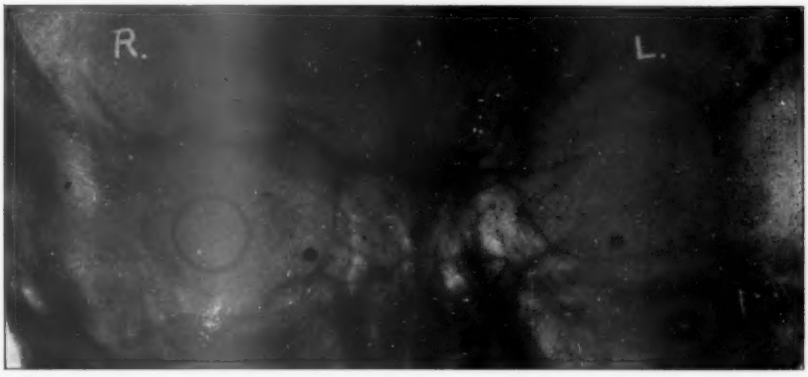


FIG. 1.—Antero-posterior view of X-ray picture with Wessely prosthesis.

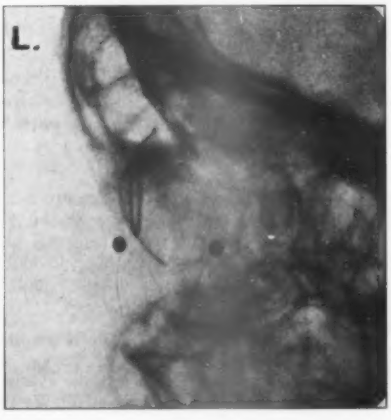


FIG. 2.—Lateral view of X-ray with Wessely prosthesis.

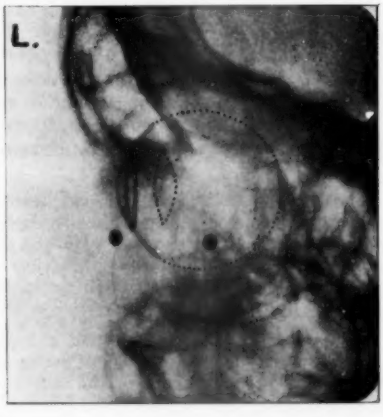


FIG. 3.—Tracing of Gullstrand eye superimposed on shadow of the prosthesis.

some time, and have found it difficult to localize foreign bodies in the posterior portion of the eye by this method. In doubtful cases I have added thereto a tracing of the Gullstrand eye which is applied to the X-ray picture as indicated by the prosthesis. (See Figs. 1, 2, 3.) Precautions must be taken that the prosthesis fits closely to the eye during the X-ray examination, and does not slip into an oblique position.

The method is not very accurate, but when complex methods such as Sweet's are open to so great an error a simple method has much to commend it.

The changing face of sympathetic ophthalmia.—While the ætiology of sympathetic ophthalmia remains the subject of discussion, the prognosis, which is important from the legal aspect, seems to be changing. Many registrars will no longer agree to a settlement for loss of an eye until they have the assurance of a consultant that there is no risk of sympathetic ophthalmia. The cases of this disease under my care during the last few years have led me to conclude that either the prognosis of the disease is very different from what was taught formerly, or else the establishment of the diagnosis from a legal point of view is not so simple as I had previously considered. These two questions are inter-dependent, and now that it is generally recognized that sympathetic ophthalmia may occur up to a month or six weeks after excision of the exciting eye, it becomes a question as to how long this period may be extended without considering that a second cause may have intervened. Examination of the eye reveals a cyclitis with a capacity for recurrence. The appearance of the deposits differs in no way from those of any other cyclitis. While there are still among us those who use the blood-count as a precautionary measure in excluding sympathetic ophthalmia, I wonder if there are any here who would offer a blood-count as contributory evidence in a court of law that cyclitis must be sympathetic in origin ; I personally would not dare to do so.

During my training, sympathetic ophthalmia was always represented as a peculiarly hopeless and fatal disease. The prognosis, however, now seems to be altering. It seems possible that most of the cases previously diagnosed as sympathetic irritation, which recovered spontaneously, were really slight attacks of sympathetic cyclitis, which are now recognized for what they really are, by the increased use of the slit-lamp.

Gifford's (*Nebraska Medical Journal*, November 1929) figures show that out of 27 cases, eight patients regained normal vision, eight 0·75 of normal, two 0·1 of normal, and the rest less than this, i.e. 66% of them finished up with quite useful vision. The other figures which I found striking, are that out of 156 cases of this disease, collected by De Grósz, 10% of them were not due to trauma at all in the ordinary sense, but followed routine operations. I have had three cases of sympathetic ophthalmia of interest in this connexion.

I.—A collier with traumatic detachment of the left retina and a certain amount of iris atrophy was treated by Gonin's operation. There was considerable reaction in the first week after operation and much œdema of the lids. The eye settled down in ten days, and at no time was any K.P. detectable in it. Six weeks after the original operation K.P. developed in the other eye. This eventually responded after six months' treatment, during which he was given one course of novarsenobillon and one of tuberculin (T.R.).

II.—Another young miner had a typical hypopyon ulcer, which eventually required Saemisch section. At the end of seven weeks, the eye still being irritable, excision was performed. K.P. developed in the remaining eye ten days later, and the patient returned from a convalescent home with sympathetic ophthalmia. This case responded in four months to novarsenobillon. The remaining eye in this Case and in Case I, are apparently normal, with $\frac{6}{9}$ vision.

III.—An old man had one eye slightly injured, and developed acute glaucoma—which responded to eserine. A hyphæma followed trephining, and five weeks later the eye showed blood-staining of the cornea, and a cataract developed. Excision was performed and on the following day K.P. developed in the other eye. The patient was sent to the venereal disease treatment centre, from which a note was received, stating that he was a known case of aortitis. The cyclitis disappeared in five weeks under treatment by novarsenobillon.

CERTAIN INTERESTING TRAUMATIC SYNDROMES

Disseminated subepithelial cataract of Vogt.—This condition was first described by Vogt in 1923 as occurring after iridectomy for glaucoma. It appears liable to occur after any trauma of the eye in which the tension is raised, including burns. Van Lint describes a case with a corneal burn caused by soldering flux. Multiple white spots are observed located in the capsule, more marked in the axis than the periphery of the lens of a sharply limited surface, and of an intense whiteness recalling polished ivory. They may disappear or get smaller, and become buried in the lens, even in a patient as old as 58. I have observed them several times in workmen after injury, including a case in which the ordinary type of traumatic cataract was present. In one of the cases in which they occurred, vision was certainly worse than the appearance of the eye would have led one to believe, and they may—although a non-progressive condition—provide an explanation of relatively poor vision in an eye that otherwise would appear to be fairly normal, namely, that there has been a period of high tension in addition to other injuries.

The anterior segment syndrome.—Another syndrome in which the vision is rather worse than the injuries would suggest has been described by Fraenkel as the anterior segment syndrome. He describes an eye in which there is a small iridodialysis with a subcapsular opacity in the lens through the edge of the pupil. A small fold situated near the greater arterial segment of the iris, and a variable depth of the anterior chamber, usually accompanies this. The indication is that there has been a marked degree of subluxation of the lens. The fundus appears normal, but in contradistinction to the posterior segment syndrome of Lagrange, the vision is disproportionately bad, and in all except one of the cases he describes there was between $\frac{1}{20}$ and $\frac{1}{50}$ of normal. I have seen two such cases following a blow, and had it not been for this account, would have found it difficult to believe that the condition was as poor as the patient made out.

Retinitis sclopeteria.—The effects of indirect trauma on the posterior segment of the eye due to penetrating injuries of the orbit, have had an interesting addition in the form of retinitis sclopeteria, i.e. retinitis from a firearm injury. It consists of hæmorrhage and whitish patches in different parts of the fundus, and I have seen it once in an injured eye following a boiler explosion in which a foreign body injured the orbit.

Unusual cases.—Retinal burns from pyrometry: A youth aged 20 was engaged in observing a furnace through a red glass and comparing its brightness with that of a glowing platinum filament, interposed between the glass and the furnace. After some months he developed a hole at the macula in the eye employed for this purpose, and was awarded a declaration of liability on these grounds. The vision in the eye was reduced to less than $\frac{6}{60}$.

Mr. Montague Hine: Disability is officially defined in terms of reduced earning capacity, the earning capacity not to depend on the chance of a disabled man getting employment in the open labour market, but on the supposition that he can at any time get a job suited to his capability for work. I doubt whether referees and assessors work strictly on this rather heartless definition, and should like to hear whether they expect us to do so when they ask our opinion as to the amount of disability.

Is no account taken of the fact that at least some insurance companies demand a higher premium from employers engaging workmen who are blind in one eye, and have been known to dispute cases in which there has been non-disclosure of this fact?

What extra degree of disability, if any, should be added when a man has to use a glass eye, as opposed to a man who has a perfectly normal looking eye, blind from a concussion optic atrophy ? How is it that a dense central corneal nebula, with some binocular peripheral field available, often brings a man more compensation than he would have if he lost his eye ?

Since disability after injury largely depends on the presence or absence of binocular vision, and any patient who has had binocular vision is seriously handicapped practically and psychologically by having to switch over to monocular vision, it is important to establish whether or no that patient has previously had binocular vision. I do not myself believe that anyone who has been used to two-eyed vision up to adult life is ever quite so skilled at any job, or at any rate is so quick at it, as he would have been with both eyes. I always feel that I need proof that some exceptional patient who does all things as well with one eye as he did with two, did not always have monocular vision, say from an unnoticed alternating strabismus. At the same time there is no doubt that young people can fairly readily adapt themselves to one-eyed vision, whereas most people over 45 find it very hard to do so. The will to make attempts is important, and is seldom present till compensation has been awarded. It is against a man's interest to prove that he is capable of going up a ladder or walking along a plank, after he has lost an eye, until his claim has been settled.

I have found it dangerous to assume, as is not uncommonly done, that anisometropic eyes are of little assistance to a normal fellow-eye. It is rather surprising how often one finds that an uncorrected anisometropic eye with, say, less than $\frac{6}{60}$ vision, gives binocular vision on a stereoscope. I think all patients with two eyes should be tested on a stereoscope.

In spite of the wage test being the only criterion of the degree of incapacity in the eyes of the law, we are not unfrequently asked what percentage of incapacity exists. This is often a difficult question, but on the Continent it is easy to answer, as everything has been tabulated on a scale, varying from 33% for loss of one eye in skilled workmen, to 25% in unskilled, and 15% for $\frac{6}{60}$ in an injured eye, down to 0 for $\frac{6}{12}$ vision. If the uninjured eye is defective the percentages are correspondingly higher. Basing everything on central vision without taking peripheral vision into account, these estimates are not entirely conclusive, but they may sometimes be found a useful guide if one is pressed for a decision.

Some of the difficult cases are those with variable vision, due, say, to vitreous opacities or subluxated lens. While these patients are sitting quietly in a chair, looking straight ahead at the test types, their vision may be $\frac{6}{18}$, but when they move their eye about as they would be during their work, it may go down to $\frac{6}{60}$ or less. Obviously the true vision for assessment is the lowest and not the highest degree, and it must always be remembered that a variable vision is much more upsetting to patients' peace of mind and equilibrium in general, than a permanently but stably impaired one. Any eye with impaired vision from retinal or vitreous changes is much handicapped and dazzled by bright light, and it is well to remember this when testing, and to try the vision under varying illuminations, not of the test types but of the room.

Mr. Harrison Butler : I must emphasize the necessity for using the slit-lamp in compensation cases. We can by this means unmask a malingerer who might otherwise succeed in his deception.

In one case a foreign body was removed from the anterior chamber. The lens was cataractous and compensation was claimed for the loss of the eye. Examination showed that there were two scars on the cornea, one a perforating one, the other non-perforating. The slit-lamp showed that the corneal parenchyma was clear and

normal-looking between the scar of entry on the anterior surface and the scar of exit on the posterior surface of the cornea. After a recent accident there is always a visible track from scar to scar through the corneal tissues. It was obvious that in this case the wound was an ancient one, probably several years old. It was discovered that the man had attended the hospital seventeen years previously, and that there had been a perforating wound. A skiagram had been negative, and the Haab magnet had failed to remove a fragment of metal. But the apparatus used at that time was a poor one, and it is a commonplace that failure to remove a scrap of metal with the magnet is no proof that there is not one in the eye. At the Birmingham Eye Hospital every foreign body removed from the interior of the eye is, for medico-legal reasons, put into a small envelope, labelled, and filed. In the case quoted I obtained the foreign body and found that it was a friable mass of iron oxide. Originally this bit of steel had been embedded in the lens. After some years the lens had become partially absorbed and the foreign body had tumbled into the anterior chamber where it was seen and removed. Nothing more was heard of this attempt to obtain compensation for an injury seventeen years old sustained during employment by a different firm.

In another case an eye had been scratched with copper wire. There was a greenish suture-cataract in the eye and a claim for compensation was made on the assumption that the green cataract was caused by perforation with a copper wire. The slit-lamp showed that there was no perforation and that the cataract was a suture cataract of the adult nucleus. The claim for compensation was dropped.

The problem of the one-eyed seems to depend largely upon the psychology of the individual and the age at which the eye was lost. One man loses an eye and in a short time is back at his work with no apparent loss of efficiency. Another persuades himself that he will never be able to work again, but his disability may disappear after his compensation has been liquidated by a lump-sum settlement.

The medical man who examines these cases is often asked to specify suitable work. In one of the tables shown by Mr. Foster the occupation of a blacksmith is scheduled as suitable. I regard all work which calls for a rapid judgment of distance as unsuitable. Such an occupation is " packing " when the workman has to drive in nails all day long, and among especially unsuitable occupations I should place that of the blacksmith. I should be sorry to be holding a set when the man who was striking with a sledge-hammer had recently lost an eye. On the other hand we find a county cricketer, who lost an eye through an accident in the autumn, playing for his county next spring, fielding at slip, and making good scores. It makes a great difference whether the lost eye is the master-eye or not. I find that I can catch a ball without much difficulty if I close my left eye, but I miss it every time when my right eye, the master-eye, is closed.

A man who has lost one eye in a machine factory owing to the entry of a piece of steel is more liable to lose its fellow than the man with two eyes is to lose one. I have no statistics on the subject, but I have been impressed with the number of men who have had foreign bodies removed from both eyes by the magnet. The one-eyed man gets closer to his machine, and turns his head so that the single eye faces the work, and is especially liable to be wounded.

During the War I came to the conclusion that women were more liable to get foreign bodies in the eye than men were.

Mr. Collyer Summers: I propose to deal only with cases in which the loss of the vision of an eye has occurred. There is only one answer to the question as to when a man is fit for work, and that is " as soon as it is possible for him to work without detriment to himself." The decision as to when this is the case should rest with the

medical officer who is treating him. There is a great deal of misunderstanding of the Workmen's Compensation Act, particularly in confusing it with common law. The law enacts that when a person is injured through another individual's negligence he must be compensated for that injury and compensated heavily. The basic principle, however, of the Workmen's Compensation Act is totally different. It is to compensate a workman for loss of earnings while he is totally or partially incapacitated as a result of an injury sustained in the ordinary procedure of his daily labours, and a weekly sum is awarded. When he has recovered sufficiently to do some work he can then take on a job at perhaps a lower rate of pay and weekly compensation is awarded for the deterioration in his earning capacity. Full compensation being only 30s. per week, it, therefore, follows that the sooner the man can get back to work, even on partial compensation, the better for him, and the sooner will he get his full pre-accident wage, and be reinstated in the labour market. Another false impression appears to be that an injured man *must* not return to work until he has been compensated for his injury by a lump sum. A lump-sum settlement can of course be privately arranged between the parties concerned and is subject to approval by the court. In " one-eye " cases when a man has returned to work he gets his wages and a declaration of liability if weekly compensation has been stopped, which declaration enables him to make a claim upon his employers at any future date if he falls out of employment, suffers from any relapse of the injury, or becomes unfit for work, indirectly owing to the injury. Yet another misconception is that entertained by most earnest and kindly members of our profession, with regard to insurance companies, who feel that the companies attempt to evade their responsibilities by every possible trick that can be imagined, whereas the fact is that they meet their obligations justly and honourably. The effects of these misconceptions upon a young and earnest house-surgeon are far-reaching. It is apparently by no means uncommon for a man to continue to be certified as unfit for work long after he has recovered—always with the idea that it is to the man's advantage, to enable him to obtain a settlement. Another cause of prolonged certification of unfitness is to be found among hospital out-patients. A patient comes for his weekly or fortnightly certificate which is continued indefinitely, owing to rush of work, without sufficient check as to its correctness. If the patient has been kept off work much too long and an issue is brought to court, the judge is then faced with a man who is fit for work but whose own doctor is stretching a point, as he thinks, in the patient's interest, and the result perhaps is the decision that the man is not only fit for his work but has been so for some time. The nett result, strictly according to the law, is not only that he loses his action and is sent back to work, but that even his declaration of liability is lost. The gross injustice of this is obvious to everybody. A declaration is more often than not presented gratuitously by an insurance company on winning such a case, and I am pleased to say that I heard one judge state in court that he would never allow a " one-eye " case to go without the award of a declaration of liability. Another effect of this so-called kindness is that solicitors of ill-repute, of which it appears some yet remain, are able to over-persuade a surgeon, against his better judgment, to state that a man is unfit for work, on the ground that he must not work until his " case is settled ", and thereby institute proceedings when there is literally no case at all. The result upon the patient when the case is lost is pathetic. The factor of disfigurement or mere loss of an eye is well exemplified in the case of Ball *v.* Hunt, recorded by Willis. I have cited this, which may apply to every one-eyed man who may lose his job through no fault of his own and have difficulty in finding another, owing to the effect on the labour market, of the fact that he is only one-eyed apart altogether from his physical ability to work. Clearly it is advisable for the man to return to work as soon as possible, from a wage-earning point of view, and it will be conceded that employment of some sort for a

one-eyed man is very good for him, both from the point of view of training him for monocular vision and also from the psychological standpoint. To rectify some of the grosser errors of long certification that one sees at present, I would suggest, firstly, that a greater interest should be taken in these cases by the senior members of our profession—who frequently relegate the whole of this side of their hospital work to junior assistants—and, secondly, that the larger hospitals should adopt the plan, now in process of evolution at neurological hospitals, of establishing an occupational therapy clinic. In most instances patients could go to the clinic about a month after the loss of the eye and the result of the tuition would be, I think, that the time taken for adaptation to monocular conditions would be shorter than it often is at present, and far more satisfactory in every way. It would also prevent the idea which appears prevalent among poorly-paid labourers that to be on compensation is a form of retirement. Another type of man who would be greatly benefited is the one to whom the shock of accident and consequent excision was great, and who forms the subconscious or even conscious opinion that he will never be able to obtain work again or to do a job if one were offered to him.

The following cases were shown :—

Cavernous Hæmangioma of the Right Orbit, Removed by Krönlein's Operation.—H. B. STALLARD, M.D., F.R.C.S.

W. S., male, aged 36. Sugar-factory worker.

17.2.37 : Attended the Royal London Ophthalmic Hospital, complaining of gradual failure of right vision for nine months.

On examination.—R.V. : Counting fingers at 1 m. Proptosis upwards and forwards. Papillœdema in upper half of optic disc and extending along the papillo-macular bundle. Retinal veins of normal size in lower half of retina. Movements normal. Pupils equal and active to light and accommodation. Right field full, blind spot enlarged ; compatible with papillœdema. All investigations negative. Left eye normal.

Pre-operative diagnosis.—Neoplasm of the orbit, outside the optic nerve and its sheaths, within the muscle cone and below the optic nerve.

Operation (Krönlein's).—At St. Bartholomew's Hospital. A hæmangioma 2·5 × 2·1 × 2·1 cm. was found within the muscle cone, wrapping round the optic nerve below and projecting upwards on its nasal side. Removal was effected by gentle separation with the gloved forefinger, and the neoplasm was delivered below the optic nerve.

Pathological diagnosis.—Cavernous hæmangioma. A few vascular spaces have a coil of plain muscle fibres in their wall, suggesting a venous origin.

Post-operative condition.—The right pupil was dilated and had a sluggish contraction to light.

Abduction has been recovered but is still limited, and there is diplopia on looking to the extreme right. The patient says that this does not worry him. Other ocular movements have been unimpaired. The central retinal vessels were undamaged. The papillœdema subsided and had completely cleared up in six weeks. The right vision is $\frac{6}{9}$ and the visual field is full.

Bilateral Pemphigus of the Conjunctiva.—O. GAYER MORGAN, M.Ch.

The patient is a man aged 70. Gingivitis developed three years ago, and he then began to have trouble with his eyelids. When I first saw him a year ago, there were small blisters on the gums. There was no disease of the buccal surface of the cheek, or of the nasopharynx or nose. The fornices of the conjunctiva were obliterated, and the corneæ were covered by a thick, viscid, tenacious secretion. The right cornea was vascularized and opaque; the left was partially affected in the same way.

I took some mucous membrane grafts from the lip, for the upper and lower fornices, sewed the edges of the graft to the edges of the incisions made to release the lids from the globe—taking a mattress suture through the middle of the graft, and out through the skin of the corresponding lid. The grafts took very easily and the cornea became brighter, and had a more natural moisture.

The patient can see to walk about and read again. He has been comfortable for six months, but the corneal vascularization is now increasing, and the graft is not so mobile as it was before. The shrinkage is affecting the graft as it affected the normal conjunctiva.